the
UNIVERSITY
of
TORONTO
MEDICAL
JOURNAL

JAN. 1966 VOL. XLIII NUMBER 3

CLINICAL THERAPEUTICS

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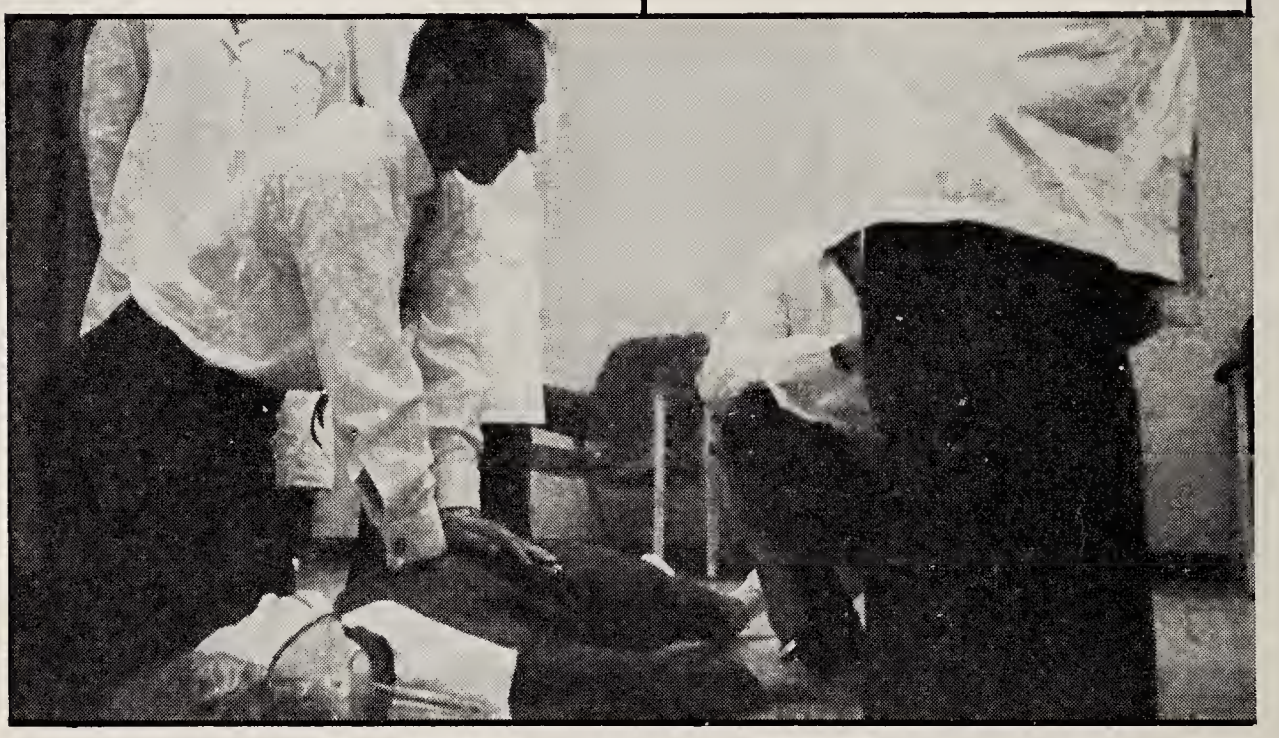

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Established December 1923
An Undergraduate Publication

Volume XLIII
Number 3
January 1966

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This Journal is published five times a year from November to March, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

SUBSCRIPTION RATES: $4.50 for one volume of five consecutive issues. Single copies, $1.00.

MANUSCRIPTS including references and footnotes should be typewritten double spaced on one side of the paper. Articles should not exceed 3,000 words. Canadian Press (American) spelling is to be used. References should be kept to a minimum, and should be cited numerically in order in which they appear in the text.

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Editorial

How many times during our clinical years in Medicine have we heard the words "one in a million" or "you will never see this again"? This invariably provokes the student remark of why don't they show us the common material first. I believe that there is a fault here and it is that insufficient emphasis is placed on the more practical aspects of Medicine at the University of Toronto.

Ideally, the answer would be a major revamping of the course but a few simple things could be done which would probably be sufficient and still leave adequate time for the more academic material.

One idea would be to increase the amount of time a student spends in the Out Patient Department. The present plan could be expanded to not only increase our time there in fourth year but also to incorporate third year students in the program. Time in this department not only gives a student a better idea of how to approach and treat the common types of problems he will face in practice but also shows the social and economical aspects of Medicine with which he must learn to cope.

Another idea would be to have fourth year students spend three or four days, in their final year, while on their Medicine or Surgery term, in the office of one of their staff men to see what his common problems are and how he handles them.

In place of this or, better yet, combined with it a week at the end of the third year of Medicine in the home or hospital of a general practitioner, in a small town or city, would be an invaluable addition to the course regardless of whether you intend to specialize or not. If you intend to enter general practice you would have a chance to observe a functioning practice with its typical patients, problems and rewards. If you intend to specialize, it would help to give you a better understanding of the pressures, equipment, lab. facilities and work load of the general practitioner and because of this, help towards the establishment of a better rapport in later life between you, as a specialist and the family doctor.

The central theme to this particular issue of the Journal is one of interest plus practical application. The article on steroids outlines the physiology in part I and then applies this knowledge in part II under some of the common therapeutic uses. Similarily the article on hypertension is set up to show that even though the surgery itself must be done by the specialist the general practitioner must be the one to suspect the lesion. Athletic injuries is strictly a practical article that should be useful to any doctor who intends to be a general practitioner or a team physician for any sport. New concepts in shock was written because the subject is so controversial to-day. If the new theories are correct a fundamental change must be made in our thinking and treatment of shock regardless of our particular branch of Medicine.

Again, haemolytic disease is one that must be dealt with by the G.P. as well as the obstetrician. The initial work and suspicion of this disease must be made by the family doctor and the newest method of treatment and how it works must be known by him so he can pass these patients on to the right areas for assessment and treatment, if necessary.

This is my idea of how Medicine could be improved here and also how the articles in this issue were designed to show that practical material can be presented in such a way as to be as interesting as the rarest flower of Medicine.

D.C.C.

New Concepts In Shock Therapy

J. Boyce 6T6

No subject in medicine is more controversial than the therapeutic measures of shock. Much of the controversy has arisen from an ignorance of the pathogenesis and pathophysiology of shock, and terms such as "irreversible" are used without full understanding of their true meaning. Recently much work has been done to reveal the altered physiology in the shock patient; and new, and often times controversial therapeutic measures are offered on the basis of these findings. These new methods of treatment are, to a large extent, directly antagonistic to the conventional approach; but when theoretical, experimental and clinical data are available to approve of the former and refute the latter then convention need not be honoured. It was largely due to work of Lillehei, Fine and Nickerson that the use of VASODILATORS was initiated as a means of treating clinical shock, and the contraindications of VASOCONSTRICTORS, like nor-adrenaline, firmly outlined. However, as we shall see, this concept is not without contest, and vasoconstrictors are still widely used in most forms of clinical shock. The proponents of this form of therapy argue that vasoconstrictors will maintain the blood pressure close to physiological levels preventing its decline as seen in shock. Much of the present discussion will attempt to outline that treating the blood pressure is not tantamount to treating the patient, and, that by strictly maintaining so-called normal blood pressure readings with vasoconstrictors, more overall harm may be done to the patient than any transient good.

Consider the altered physiology in a patient who has lost a considerable quantity of blood: he will be pale, have cold sweating extremities, a rapid heart rate, collapsed veins, slow capillary filling and will be oliguric; in other words he will have the signs of excess sympathetic nervous stimulation.[1] In the dog, an analogous situation can be created by withdrawing 50% of the blood volume.[2] The decreased circulating blood volume sets the sympathetic nervous system into play via the baroreceptors in the carotid sinus and aortic arch. Circulating catecholamines are increased in concentration[2,3] and act in a manner to preserve adequate blood flow to the heart and brain. Adrenaline acts on the heart to increase the rate and strength of contraction and its relative, nor-adrenaline, acts on the peripheral vessels to increase the resistance to flow. The net effect is the maintenance of adequate pressure to perfuse the myocardial and central nervous tissues. The action of nor-adrenaline, however, is not confined to the precapillary sphincters, but also has a marked effect on the capacitance vessels as shown in figure 1.

The significance of the action of nor-adrenaline on the capacitance vessels is that the hydrostatic pressure within the capillary bed is increased above normal values and this results in the transudation of fluid from the vessels to the interstitial spaces. This further decreases the circulating volume and the shock is aggravated.[3,4] In this manner it is possible that shock can breed more shock, and a vicious cycle established leading to the irreversible state.

The action of nor-adrenaline on the pre-capillary spinctors is most marked on the arterioles of the abdominal viscera,[5] and to a slightly lesser extent on those of the skin. The cerebral and coronary vessels are relatively

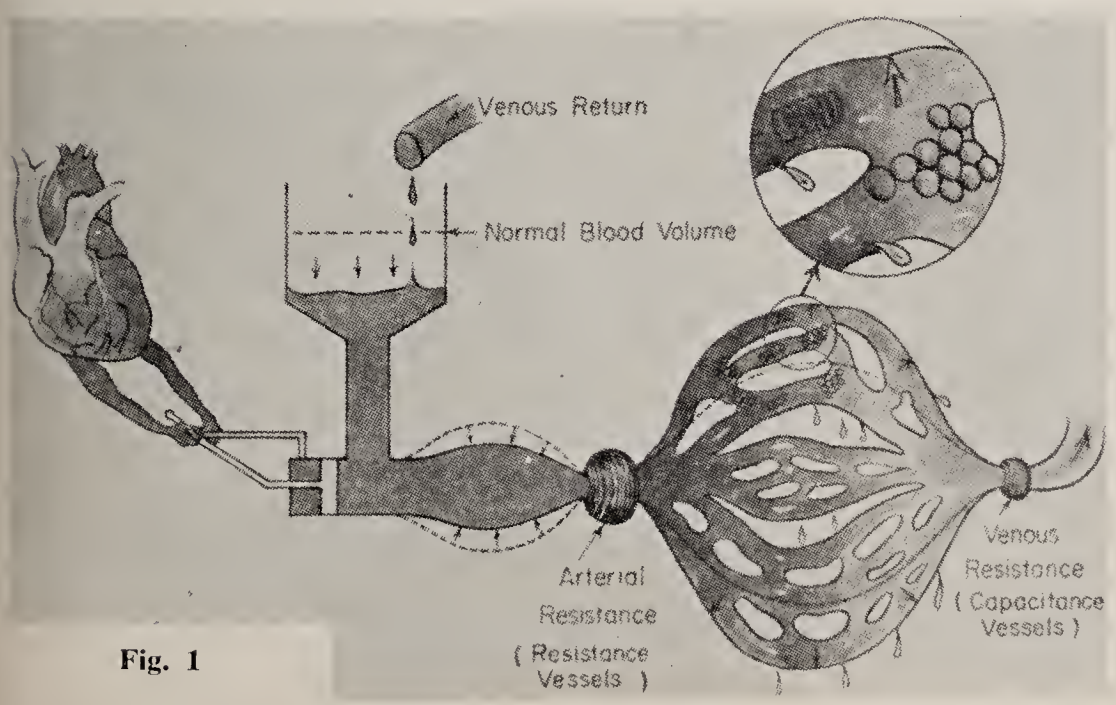

Fig. 1

Figure 1. The action of nor-adrenaline on both the pre- and post-capillary vessels resulting in transudation of fluid into the interstitial spaces. See reference 2.

unaffected by this vasopressor action. Blood, therefore, is diverted away from such organs as the liver, kidney, spleen and gut for its use in heart and brain metabolism. Dr. Lillehei suggests that this arteriolar constriction can so impair the blood supply to an organ, that cell death due to ischemia occurs within the parenchyma. This cell death within vital organs is the basis of irreversible shock.

EXPERIMENTAL IRREVERSIBLE SHOCK

Lillehei's experimental animal was the dog. The organ most severely affected by the marked vasospasm following haemorrhage was the gut. If the animal was kept in shock (i.e. was bled until the mean arterial blood pressure was 35 mg. Hg.) for a period of 4.5 hours, it died in spite of reinfusion of the blood. Death was usually heralded by a bloody diarrhea and at autopsy, the gut was found to be a mass of haemorrhagic necrosis. Theoretically the shock state had caused vasospasm of the arterioles of the splanchnic area and the ischemia had resulted in tissue necrosis of the bowel. When the blood was replaced into the circulating volume if merely extravasated into the interstitial spaces and ultimately, into the bowel lumen. Therefore, no amount of blood replacement could save the animal. By definition, after 4.5 hours of a decreased circulating blood volume, the dog had reached irreversible shock, and transfusion of an adequate volume of blood failed to prevent death.

In order to single out the gut as being significant in the pathogenesis of shock, Lillehei devised experiments to keep the bowel well perfused with blood, and, at the same time, subject the rest of the animal to the conditions of haemorrhagic shock. By perfusing the superior mesenteric artery of the experimental animal with a blood supply from a donor dog, the animal, when bled an equal amount as before, did not reach the irreversible state and subsequent transfusion resulted in a healthy animal.[2] In addition, it has been shown by other workers that the irreversible state can be hastened when means of augmenting the sympathetic activity are employed. For example, the reflex vasoconstriction to nociceptive stimulation in animals, previously subjected to haemorrhage, leads to death at residual blood volumes otherwise compatable with life.[6]

Under conditions of such altered physiology of the precapillary arterioles, the administration of L-norepinephrine would only enhance the vasoconstriction, augment the tissue necrosis and hence hasten the animal to the irreversible state. These hypotheses were confirmed by experimental observation.[2] The question is: if, in haemorrhagic shock, pressor agents appear to be contraindicated, then what measures can be taken to prevent this irreversible state? For human therapy, Lillehei recommends fluid replacement in the form of low molecular dextran or other plasma expanders, and massive dosages of glucocorticosteroids, i.e. 1 gm. hydrocortisone I.V. The mechanism(s) of the beneficial effect of steroid administration is not known but his experimental observations reveal that there was reduced or absent bowel necrosis when the animals were sacrificed at the time when the bloody diarrhea was expected, and in most cases, irreversible shock was prevented in the face of standard lethal haemorrhage. By an unknown mechanism, steroids appear to act in an anti-adrenergic way at the arteriolar level to maintain adequate tissue perfusion without lowering the diastolic blood pressure.[2,7] In comparison, as mentioned before, his experiments using vasopressor agents only precipitated the onset of bloody diarrhea and the irreversible state such that significantly less than 4.5 hours of reduced blood pressure was required to kill the animal.[2]

Chein did some interesting experiments to qualify the observed beneficial effect of ablation of sympathetic activity in clinical shock. By subjecting both sympathectomised and non-sympathectomised dogs to acute haemorrhage, he found that he could rapidly withdraw more blood from the non-sympathetomised animals than those who had their sympathetic nervous system surgically removed prior to haemorrhage.[27] This seems to be an argument directed against the use of vasodilators in the treatment of haemorrhagic shock. He points out, however, that the role of the sympathetic nervous system in the preservation of life after acute haemorrhage, was in its cardio-tonic and vasoconstricting properties *early* after blood loss to prevent sudden fatal cerebral and myocardial ischemia. However, this beneficial effect of sympathetic activity is only for a period of 5 - 10 minutes after the onset of severe blood loss. Any prolongation of such activity is to be considered harmful.[27]

Afferent nerve stimulation will also enhance the deleterious effects of sympathetic activity and lower the tolerance to haemorrhage.[28] He suggests that the beneficial effects of adrenolytic agents, such as hydralazine, might be due to their un-uniform way of blocking the sympathetic system, so that the cardiac factors are preserved to maintain tissue perfusion, and the arteriolar factor is abolished to prevent tissue ischaemia.[29]

Recent terminology of the subdivisions of the sympathetic receptor sites, the cardiotonic properties of the adrenergic system results from stimulation of the Beta-receptors and the arteriolar constriction results from stimulation of the alpha-receptors. Adrenalin is primarily a Beta-stimulator and nor-adrenaline an alpha. To put Chein's conclusions in terms of this terminology we could say that the beneficial effects noted by Hydralazine are the result of its alpha-receptor lytic action with preservation of Beta activity.

That the beneficial effect of vasoconstriction via the sympathetic nervous system is manifested only in the early stages of shock, is further outlined by Rosenberg et al.[34] He maintains that the experiments of Lillehei and Nickerson are a real advance in our understanding of shock, but he holds that in the early stages of shock,

as when there is a sudden loss of blood, immediate treatment should be with vasoconstrictors simply to preserve blood flow to the brain and heart. This treatment is especially helpful in older patients with arteriosclerosis of their cerebral and coronary arteries. These people if ever treated with vasodilators, would surely die. However, he agrees with Dr. Lillehei, that prolonged treatment of shock with vasoconstrictors, is definitely contraindicated as it leads to massive tissue death in those areas in the splanchnic nerve distribution.[34]

FURTHER EXAMPLES OF VASODILATOR THERAPY

Nickerson presents his approach to the treatment of clinical shock by advocating phenoxybenzamine (Dibenzyline). This, drug is an anti-adrenergic compound, exerting its most marked effect at the arteriolar level, particularly in the splanchnic area. In his experiments, dogs pretreated with phenoxybenzamine then subjected to standard lethal haemorrhage, were restored to health after reinfusion.[8] These experiments were repeated by Lillehei with the same results.[2] It is suggested that because the animal was spared the deleterious effects of severe reflex splanchnic vasospasm, the viscera were kept adequately perfused and the irreversible state was prevented. Dr. Nickerson has had appreciable success with phenoxybenzamine in the treatment of shock patients. He suggests that fluid replacement in conjunction with this drug will give a better clinical result than has ever been achieved with pressor therapy. However, he emphasises that fluid replacement is manditory when using phenoxybenzamine, in order to avert fatal hypotension.[8]

Wilson et al.[15] present their findings after a clinical trial of vasodilator therapy. Nineteen patient in clinical shock, were treated in the conventional manner by using volume replacement, correction of acid-base imbalance, vasopressor agents, and where indicated, digitalis. When phenoxybenzamine (Dibezyline) was used as advocated by Nickerson[16] they noticed a lowering of systolic blood pressure, a decreased central venous pressure, increased cardiac output and stroke volume, increased urine output and a generalized improvement in the clinical condition. They emphasized that where the clinical picture failed to improve on vasoconstrictor therapy, it did so in a significant number of patients treated with Dibenzaline.[15] Wilson feels that the increased tissue perfusion allowed when the vasoconstriction is removed, is a key factor in the rapid improvement of the patient. To answer those who feel that cardiac deterioration is the prime factor in irreversible shock, there is evidence to suggest that Dibenzyline increases the cardiac output under lower left ventricular tension, therefore, reducing myocardial work.[15 18]

Chlorpromazine, one of the phenothiazines, is a relatively new drug. Its ganglioplegic, adrenolytic, antipyretic, anti-edemic, anti-convulsant, and antifibrillatory properties were described as recently as 1953 by Courvoisier.[30] Most of its adrenolytic properties appear to act in the pituitary-adreno axis, which is the body's major pathway for the physiological manifestations in response to stress. By this mechanism, when the body is subjected to a stressful situation, the end response is activation of the sympathetic nervous system, with its cardiac and vessel manifestations as described above. One of the properties of Chlorpromazine is to ablate much of this sympathetic activity. When rats are pretreated with 1-5 mg. of Chlorpromazine 20 minutes prior to induced traumatic shock, the survival rate rose from 35% in the untreated rats to 90% in the treated group.[31] Other workers have shown that the administration of Chlorpromazine after induction of haemorrhagic shock, will increase the blood flow in the superior mesenteric artery and[32] more than double the survival time of these animals. Further evidence has shown that a diuresis is established in animals so treated, in spite of the fact they were oliguric prior to treatment.[33]

In 1958 Collins et al.[34] decided to give this drug a clinical trial in the management of clinical shock. He grouped his patients into three categories: I—those requiring surgery for massive gastrointestinal bleeding; II—those in oligaemic shock from causes other than G.I. bleeding; III—those in shock which developed during the course of surgery. Of a total population of 396, 173 were treated with Chlorpromazine in divided dosages of 0.2 mg./kilo body weight plus fluid replacement, and the rest were treated in the usual manner with fluid and constrictor therapy. In the three groups which did not receive the vasodilating agent, the mortalities were 43%, 28.5%, and 53.1% respectively and in those receiving Chlorpromazine they were 27.5%, 11.6%, and 22.2% respectively. Collins feels that it is the effect of the vasodilation to the renal vessels which constitutes the key factor resulting in the observed decrease in mortality. Other clinicians have abandoned the use of Chlorpromazine in shock states because of the previously observed fatal hypotension shortly after administration but Collins holds that small amounts (0.2 mg./kilo) in divided dosages, will avoid this hazard.

THE ISSUE OF BACTERAEMIC OR SEPTIC SHOCK

Contrary to popular thinking, the problem of bacteraemic or septic shock is quite analogous to the haemorrhagic type. Much of our understanding of this subject comes from the work of Jacob Fine in Boston. According to his observations[9] and others,[10] the endotoxin released by gram negative bacteria has a very pronounced sympathetic enhancing effect, particularly to the locally secreted catecholamines (primarily noradrenaline) in the various organs such as the spleen.

To demonstrate this synergism of endotoxin and locally secreted nor-adrenaline, Fine devised experiments

wnere he surgically denervated one-half of the spleen; then, some days after the animal recovered from the operation he subsequently administered lethal dosages of endotoxin by the intravenous route into these animals, this procedure was followed by sacrifice of the dogs and a detailed gross and histological examination of the spleen.

It was found that the half of the spleen still retaining its original splanchnic (sympathetic) nerve supply, was necrotic and swollen with blood; on the other hand, the half which had had its sympathetic nerve supply removed by the previous operation, was of normal size and microscopic examination showed normal healthy tissue, devoid of any haemorrhagic necrosis.

Thus, circulating endotoxin can result in a severe vasoconstriction, both of the precapillary arterioles and of the post capillary capacitance vessels, thereby causing tissue necrosis due to ischaemia and fluid loss into the interstitial spaces. The ischaemic organ will have decreased reticulo-endothelial cell function, and, as a result the normal endotoxin dettoxifying powers of the reticuloendothelial system will be subnormal. Therefore in shock, the endotoxin causes enhanced sympathetic activity, which in turn causes constriction of the arterioles, which leads to tissue ischaemia, which result in decreased cell function, and this allows a rise to lethal levels (of endotoxin in the circulation) Fine believes that irreversible shock is the state when enough endotoxin is in the circulatory system to cause R. E. cell ischaemia. To prevent this ischaemia he surgically removed the sympathetic nervous supply to the abdominal viscera by excising the coeliac plexus. Then, when he subjected these animals to previous lethal dosages of endotoxin, irreversible shock did not occur. He postulates that because severe vasoconstriction was prevented by denervation, normal visceral perfusion was maintained and hence, R.E. cell function was preserved and was able to detoxify the endotoxin and prevent lethal levels from being attained. Fine does not describe how high levels of endotoxin can cause death, but his experiments have been confirmed by other workers,[11] who suggest the endotoxin has a direct lethal action on the alveolar capillaries resulting in massive pulmonary edema, which is often soon followed by death.[38] He suggests that any type of shock if left long enough will develop into endotoxic shock.[12] As Lillehei suggested for dogs, Fine and others[13 14] feel that in shock the bowel is a target organ for necrosis and the effective barrier between the bacterial laden bowel and the circulatory system is abolished, and massive infection ensues from this source. His experiments after bowel lavage show a decreased incidence of irreversible shock. However, other investigators have failed to observe any improvement when the fecal contents were washed from the bowel.

Granted it would be absurd to consider removal of the coeliac plexus in the shock patient and Dr. Fine is not advocating this as a means of treatment. What these experiments do demonstrate is the harmful effects of splanchnic vasospasm and point out the possible benefits of having such activity removed in conditions of shock.

THE PLACE OF VASOPRESSORS

It was mentioned at the beginning that the subject of the treatment of shock was controversial, and the proponents of vasoconstrictor therapy are not going to ignore their own experimental results. Udhoji et al.[7], maintain that carefully monitored dosages of pressor substances may be valuable in treating shock and offer experimental data to justify its use.[19 20] The shock associated with myocardial infarction is not mentioned by Lillehei, Fine, or Nickerson. Many investigators feel that pressor agents have beneficial effects in treating this condition,[21] particularly when some of these agents have significant cardiotonic properties, (Wyamine, Aramine, Angiotensin II,).

Isoproterenol (isuprel) is perhaps the most selective of the newer sympathomimetics. It restricts its stimulatory effects to the Beta-receptors and has no effect on alpha receptorsites. If this drug is used in shock of cardiac origin, particularly where bradycardia is apparent then vasodilation will result, probably secondary to the inotropic action on the heart.[39]

COMMENT

That the sympathetic nervous system may exert deleterious effects on the human system was recognised by Cannon in 1934.[22] Only recently has much work been done to try and discover what the nature of this harmful effect might be. Whether or not vasodilators or vasoconstrictors should be the mainstay of shock therapy cannot be answered here but, it can be stated, with good experimental backing that the indiscriminant use of vaso-constricting agents in the treatment of shock, can make the condition irreversible. Furthermore, there is significant evidence to suggest that the abolishment of sympathetic activity, primarily at the alpha receptor sites, coupled with adequate fluid replacement, can, and often does improve the clinical condition of the patient in shock.

SOME NEW IDEAS

Indeed the argument will not stop at the issue of the sympathetic nervous system. Former work has stressed the importance of sludging in the microcirculation[23] in the shocked animal, and in the increased tendency to form microthrombi.[24] These workers suggest that these factors may be instrumental in the pathogenesis of irreversible shock. Agents such as Low Viscosity Dextran (LVD), and systemic injections of Fibrinolysin are now being advocated as supplemental therapy. A particularly new idea is the use of high energy phosphates

in the treatment of shock,[25] but since ATP is available for clinical use only in Japan, no series is on record regarding efficacy.

I briefly alluded to those workers who feel that the heart is the key factor in the determination of irreversible shock. Guyton and Crowell[35] have done many experiments to show that the onset of irreversible shock is marked by the onset of cardiac failure as measured by increasing intra-atrial pressures. Associated with this heart failure is a marked systemic oxygen debt, i.e. there is a descrepancy between the oxygen available for body tissues and the amount required. This results in relatively more anaerobic metabolism than normal. It is suggested that lactic acid or some other metabolite from this metabolism may have toxic effects on the myocardium and cause failure. To off-set this oxygen debt, some investigators have advocated the use of hyperbarometric oxygen in treating these people. Such pressure breathing would supply maximum O_2 to the systemic circulation particularly by increasing the molecular O_2 in physical solution. But these concepts are still at the experimental stage, as there is a danger of oxygen poisoning with this method.

SUMMARY

Recent experimental investigation has been done to remove the concept of irreversible shock from the times when it was considered to be "a manifestation of a rude unhinging of the machinery of life"[37], to an expression in terms of pathology, an altered physiology. For Dr. Lillehei, the expression is linked to haemorrhagic necrosis of the bowel resulting from ischaemia: for Dr. Fine, its an overwhelming concentration of endotoxin resulting from decreased R.E. cell function; and for Dr. Guyton, it is cardiac degeneration. This, by no means, exhausts the list. From these and other investigators there have come new and radical modes of treating shock, of which the use of vasodilators is probably the most controversial.

ACKNOWLEDGEMENT

I would like to express my appreciation to Dr. Morley Sutter, Department of Pharmacology, U of T for his time and advice in preparation of this article.

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(Continued on page 122)

Surgically Treatable Hypertension

R. C. Sider, B.A., 6T6

Hypertension is one of the most common afflictions known to man. It is estimated that over one-half million Canadians suffer from this condition. It is also a most fascinating entity because of the many questions pertaining to etiology and pathogenesis that remain to be answered. No one is even sure at what blood pressure level a patient should be considered hypertensive. A good general rule is that patients who have blood pressure recordings greater than 140/90 mm. Hg repeatedly under casual conditions are hypertensive.

Hypertension is a common cause of morbidity and mortality. The heart, brain, eye and kidney are the organs most affected. Congestive heart failure, myocardial infarction and cerebral vascular accidents are the most frequent causes of death.

A useful classification of hypertension is as follows:

I. NEUROGENIC
  A. *Essential*
    1) Normotensive hyperreactor
    2) Intermittent hypertension
    3) Continuous hypertension
  B. *Malignant*

II. HUMORAL
  A. *Adrenal*
    1) Cushings's syndrome
    2) Primary aldosteronism
    3) Pheochromocytoma

  B. *Renal*
    1) Bilateral kidney disease
    2) Unilateral kidney disease

III. MECHANICAL

  A. *Coarctation of the aorta*

The humoral and mechanical causes of hypertension are much less common than the neurogenic, comprising only 10% of the hypertensive population, but these are curable in most cases. It is of great importance, therefore, that every hypertensive patient be investigated thoroughly enough to separate the "curable" ones from the more common essential hypertensives. A discussion of the surgically curable types of hypertension follows.

A. RENAL

That the kidney has had a significant etiological role to play in hypertension has been suspected by physicians for hundreds of years. In 200 B.C. a Chinese physician, Choun-You-J wrote, "When the pulse, upon depressing, is very firm and upon superficial palpation, tight, then the disease has its seat in the kidney." Richard Bright, in 1827, revived this concept and today there is no doubt that the kidney is the source of trouble in a significant proportion of the hypertensive population.

1) Incidence

It is estimated that surgically correctable renal hypertension is present in 5% of the hypertensive population. Some idea of the magnitude of this problem is gained when it is realized that 30,000 Canadians or 2,500 people in Toronto are candidates for corrective surgery.

2) Pathogenesis

The elucidation of the mechanism(s) by which the kidney causes hypertension occupies investigators in major centres throughout the world at the present time. The most widely accepted theory is that the affected kidney releases a pressor substance or a precursor which acts directly on the arterioles to produce hypertension. The discovery that a proteolytic enzyme of short life, renin, is produced by kidney tissue and that it acts on a peptide synthesized by the liver (angiotensin I) to produce angiotensin II (a powerful vasopressor) offered evidence for the theory.

The stimulus or stimuli responsible for increased renin secretion in renal hypertension has not been determined. It is believed by many investigators, however, that either renal ischemia or a change in the character of the pulsatile blood flow to the kidney is the underlying stimulus.

3) Pathology

Surgically treatable renal lesions responsible for hypertension can be divided into two broad groups;

1) those of the renal vasculature.

2) those of the renal parenchyma.

The only common vascular lesion is renal artery stenosis. Stenosis is most frequently due to an atheroma. This type of stenosis usually occurs near the aortic orifice of the renal artery and affects patients of middle age or over. Stenosis may also be caused by fibromuscular hyperplasia, a curious thickening of the walls of the renal arteries. This occurs some distance beyond the origin of the renal arteries, looks like a chain of beads with multiple stenotic sites, and occurs most commonly in young women. Bilateral stenotic lesions of either the atheromatous or fibromuscular type are not rare.

Parenchymal lesions are treated surgically by removal of the pathological tissue. The disease must be confined to one kidney to be amenable to surgery since one functional kidney must be left intact for survival. Uni-

lateral or segmental pyelonephritis is the most common operable parenchymal lesion.

4) Diagnosis

One of the most vexing problems in renal hypertension is the selection of those patients whose disease is surgically remedial. The last fifteen years has been a period of rapid advance with the development of highly specialized investigative techniques. But even in the history and physical examination of the patient, certain features should alert the physician to the possibility of correctable renal hypertension.

a) History

There are no symptoms specific for renal hypertension. It may be symptomless. The following features are, however, suggestive of renal hypertension.

i) Onset of hypertension before age 30 or after age 55.

ii) Abrupt onset and rapid progression of hypertension at any age.

iii) Sudden acceleration of pre-existing hypertensive disease.

b) Physical Examination

The only fairly specific finding in correctable renal hypertension is a continuous harsh abdominal bruit commonly epigastric and heard best on one side. One may expect to find this in approximately one half of patients with renal artery stenosis.

c) Investigations

Investigative techniques are becoming progressively better and more sophisticated. There is considerable argument about which set of investigations is most useful for any particular patient. They will be outlined here in order of their practicality and safety.

i) Urinalysis

This simple procedure is diagnostic of acute and chronic glomerulonephritis thus ruling out the possibility of surgical correction. Chronic pyelonephritis, a surgically treatable lesion if unilateral, can be diagnosed by the presence of white blood cell casts. There are no pathognomonic changes in renal artery stenosis.

ii) Intra-venous Pyelogram

Although this examination may be entirely normal in the presence of severe renal artery stenosis, three abnormailties are commonly found and the presence of any one of them is an indication for further investigation.

a) non-function in which no dye is excreted.

b) delayed excretion of dye.

c) disparity in length of more than 1 centimeter between the two kidneys.

iii) Radio-isotope Renogram

This test, developed in 1955, untilizes a very small amount of I^{131} labelled para-amino-hippurate which, after I.V. injection, is rapidly excreted by the kidneys. Gamma ray scintillation counters are placed over each kidney area and a radio-activity tracing is made as the I^{131} passes through the kidney. Different renal diseases are said to affect the resulting radiation curve tracings in characteristic ways. In the hands of experienced investigators this technique is 85% accurate in diagnosing renal disease capable of causing hypertension.

iv) Renal Arteriography

The only method of visualizing stenosis of the renal artery is by injection of dye into the abdominal aorta and radiographically following the progress of the dye through the renal arteries. Two approaches are available, the direct trans-lumbar aortic puncture and the retrograde femoral. Arteriography will almost always demonstrate stenosis when present. Unfortunately the demonstration of renal artery stenosis in a hypertensive patient is no proof that there is an etiological relationship. It is, however, a highly suggestive finding.

v) Ureteral Catheterization Studies

It was discovered little more than a decade ago that the urine excreted by an ischemic kidney differs significantly from the normal. This knowledge was utilized in the development of a test to locate the offending kidney in cases of renal hypertension. Both ureters are catheterized and under standard conditions three timed urine samples are taken from each ureter and analyzed for volume, Na concentration and creatinine concentration.

In stenosis of the main renal artery the urine from the ischemic kidney is reduced in volume by 50% or more, Na concentration is reduced by 15% or more and creatinine concentration is increased by 50-100% as compared to the healthy side.

In unilateral chronic pyelonephritis the urine from the diseased kidney is reduced in volume by 50% or more, Na concentration is equal and creatinine concentration is decreased by 50% or more as compared to the healthy side. This test is accurate in predicting a surgically correctable lesion it up to 80% of cases.

vi) Renal Biopsy

This procedure is not well established in the investigation of renal hypertension. The one potent argument in favour of renal biopsy is that when done bilaterally it may show whether the kidneys are basically normal or whether they are permanently damaged and thus not amenable to surgery.

d) Surgical Treatment

Soon after Goldblatt's classical experiments in 1934 there was a surge of interest in unilateral nephrectomy as a cure for hypertension. This procedure became very

popular and hundreds of kidneys were removed at the first signal from the sphygmomanometer. Since there were none of the highly specialized investigations now available it was inevitable that a large number of unsuitable patients were selected for operation. Indeed, as late follow-up studies began to be reported it was discovered that a disappointing 20% were cured of their hypertension. The frequency of nephrectomies progressively decreased, and it was not until the early 1950's that nephrectomy was demonstrated to be effective in carefully selected cases.

Today nephrectomy is done on patients, who, after thorough work-up, are believed to have renal hypertension on the basis of unilateral parenchymal disease or in cases of unilateral vascular disease where the vessels cannot be directly repaired. Nephrectomy now results in cure of hypertension in up to 70% of cases. Another 20% are significantly improved.

Vascular surgery is now used extensively to correct renal vascular lesions, particularly stenosis. The commonest two methods are (1) endarterectomy and (2) insertion of a Teflon bypass graft. Both methods are suitable for most vascular corrections. Endarterectomy is popular for atheroma removal and involves opening the artery, removing the plaque and suturing a small patch graft into the wall of the vessel. Teflon bypass grafts are very versatile. The graft can be used to connect virtually any large nearby artery (usually the aorta or iliac) to the renal artery distal to the stenosis by an end-to-side anastomosis. Other methods which are used include excision of the stenotic site with direct anastomosis of the two ends, spleno-renal anastomosis for left side lesions and saphenous vein grafts.

The results of corrective vascular surgery have been gratifying. Significant improvement has resulted in 60-90% of patients and most of these are permanently cured of their hypertension.

B. Adrenal

Abnormalities of the adrenal gland are not a common cause of hypertension. Since it is true, however, that almost all cases of adrenal hypertension are amenable to surgery these conditions must be thoroughly understood and searched for in the hypertensive population. The adrenal cortical causes of hypertension are Cushing's syndrome and primary aldosteronism. Pheochromocytoma is the medullary lesion causing hypertension.

1) Cushing's Syndrome

Cushing's syndrome represents the constellation of signs and symptoms arising from prolonged exposure to excessive quantities of glucocorticoids. In the years since 1932 when Harvey Cushing diagnosed this disease it has been found to be an increasingly complex entity. The following categories are now recognized:

Exogenous

(a) prolonged administration of glucocorticoid
(b) prolonged administration of ACTH

Endogenous

(a) adrenal adenoma
(b) adrenal carcinoma
(c) bilateral adrenal hyperplasia
  (i) secondary to an ACTH — producing tumour
  (ii) secondary to other tumours producing substances with ACTH — like activity (carcinoma of lung, pancreas and others)
  (iii) secondary to "hypothalamic dysfunction".

Hypertension is a feature of 80% of patients with Cushing's syndrome and may become very severe. The mechanisms which underlie the development of hypertension in this disease remain obscure. Changes in salt and water balance and in the response of the blood vessels to pressor amines are two theories which have been suggested.

a) Diagnosis

The clinical features which lead one to suspect Cushing's syndrome include striae of skin, ecchymoses, muscular weakness and wasting, compression fractures of vertebrae, moon facies, buffalo hump and hypertension. Psychosis and diabetes are noted in some cases.

The diagnosis rests on the demonstration of increased production of glucocorticoid by the adrenal gland. Twenty-four hour urine specimens analyzed for 17-hydroxy corticoids will amost always make the diagnosis. To determine which of the several varieties of Cushing's syndrome the patient is suffering from other tests are necessary.

i) Diurnal rhythm

Normally twice as much glucocorticoid is produced and excreted from 7 A.M. to 7 P.M. as from 7 P.M. to 7 A.M. This diurnal variation is often lost in Cushing's syndrome.

ii) Urinary free hydrocortisone

In normal patients most hydrocortisone is plasma bound. When hydrocortisone production is markedly elevated the plasma binding potential is saturated and a large proportion is free in the blood and thus excreted as free hydrocortisone in the urine. This test is sensitive and detects early increases in glucocorticoid production.

iii) ACTH Response

After baseline determinations for 24 hour 17-OH and 17-Keto steroids have been done 50 units of ACTH are infused during the first 8 hours of two consecutive

24 hour periods. The urinary 17-OH and 17-Keto steroids are measured for each 24 hour period. Lack of response indicates either an atrophied gland or an autonomous gland.

iv) Dexamethasone suppression test

0.5 mg. dexamethasone is administered orally every six hours for a 48 or 72 hour period. Normally this will suppress endogenous glucocorticoid production and 24 hour values for urinary 17-OH and 17-Keto steroids will fall dramatically. Patients with autonomous adrenal glands will not suppress at all. Patients with a high "setting" of the hypothalamic center will require much higher doses (2 mg. q.6.h.) for adequate supression.

Other tests of value include a white blood count to show a low absolute eosinophile count, and an intravenous pyelogram to demonstrate supra-renal distortion or a mass.

b) Treatment

The recommended treatment for Cushing's syndrome varies with the type and severity of the disease. If hypertension is severe, regardless of the type of Cushing's syndrome present, radical subtotal or total adrenalectomy is advised. Results with less than radical surgery have been discouraging. Adequate replacement therapy is an integral part of the total treatment. On the day before operation 100 mg. cortisone acetate is given intramuscularly. On the day of operation 300 mg. hydrocortisone and 150 mg. cortisone acetate is given. The dose is then tapered in the post-operative period until at the end of three weeks the maintenance dose of 37.5 mg. cortisone acetate and 0.1 mg. fluorohydrocortisone daily is reached.

The results of this treatment vary with the underlying condition. Hypertension often recurs in patients with a malignant tumour of the adrenal cortex because of metastases. In those with benign adenomas results are good; one recent report of cortical adenomas indicates a complete cure of hypertension in 11 of 13 patients. Of those patients with bilateral hyperplasia 50-70% may be expected to be cured of their hypertension. If, in any of these conditions the hypertension has progressed pre-operatively to the malignant phase with renal complications, the prognosis is very poor.

2) Primary Aldosteronism

Primary aldosteronism may be defined as an inappropriate excessive secretion of aldosterone resulting in a syndrome of hypertension, renal wasting of potassium, hypokalemia and alkalosis. Usually the disease is due to single or multiple small adrenal adenomas. It was first described by Conn in 1955 and since then has been recognized with increasing frequency.

a) Diagnosis

Although there may be a complete absence of symptoms the commonest are muscle weakness, nocturnal polyuria, headache and polydipsia. The severity or duration of hypertension is not an aid to diagnosis. Physical examination will almost never reveal a supra-renal mass since aldostreone-secreting adenomas usually weigh less than six grams and therefore are not palpable.

Laboratory studies are the key to diagnosis. A persistently low serum potassium level in the absence of other causes (most commonly chlorothiazide diuretics) is the single most important abnormality. Urine potassium levels remain high in spite of low serum potassium. Usually the urine has a high pH and a low specific gravity. Serum CO^2 content is often raised to values of 32-38 mEq./litre. The most direct diagnostic test is the measurement of serum and urine aldosterone levels. At the present time, however, this is a very difficult test and few centres are equipped to conduct it.

One other difficulty in diagnosing primary aldosteronism is the occurrence of the well recognized entity, secondary aldosteronism. This condition has all of the features of the primary disease except that it is secondary to renal hypertensive vascular disease. The distinction can be made if it is remembered that, (1) most hypertensive patients with papilledema or elevated blood urea nitrogen levels have secondary aldosteronism; (2) secondary aldosteronism only causes mild or borderline alkalosis; and (3) in patients with hypokalemia and evidence of unilateral renal arterial obstruction aldosteronism is probably secondary.

b) Treatment

The treatment of primary aldosteronism is removal of the offending tumour. Operation should be performed only in clearly diagnosed cases. It is usually possible, after carefully examining both adrenal glands at surgery, to locate and remove the tumour(s) and leave the rest of the gland intact. If no adenoma is found the larger adrenal gland is completely removed and sectioned. If the tumour is still not found one half of the remaining gland is removed and sectioned. A further one quarter of the gland is removed if necessary. By this procedure 90% of the adrenal tissue has been removed. Enough functioning tissue is left for adequate adrenal functional but there is a 90% chance that the offending tumour has been removed.

The results of surgery are excellent. Almost every case of carefully selected primary aldosteronism becomes normotensive after surgery. A relevant observation is that although the biochemical abnormalities revert quickly to normal the blood pressure may gradually fall toward normal over a period of months.

c) Normokalemic Primary Aldosteronism

In the past year the concept of normokalemic primary aldosteronism has been proposed by Conn. It is his belief that hypertension is the first clinical manifestation of primary aldosteronism and that the characteristic biochemical changes may not appear until many years later or, indeed, never occur. Therefore these

people are indistinguishable from the population of essential hypertensives. He further maintains that 20% of patients with the diagnosis of essential hypertension actually have a small functioning adrenal adenoma and are suffering from normokalemic primary aldosteronism. Conn recently developed a test which he believes is specific for this disease. He has found that although the electrolytes are normal the plasma renin level is markedly reduced while the plasma aldosterone level is significantly elevated. The next few years will determine the validity and impact of this discovery.

3) Pheochromocytoma

This is a rare cause of hypertension. It is a catecholamine-producing tumour arising from the chromaffin cells of the sympatho-adrenal system. Eighty percent of pheochromocytomas arise from the adrenal gland and a further 15% are located in the pelvic or abdominal regions. They are rarely malignant. These tumours produce epinephrine and/or norepinephrine and it is the release of these compounds which gives rise to the typical paroxysmal attacks.

Diagnosis depends upon a high index of suspicion in patients who present with any or all of the following signs and symptoms: 1) excessive sweating, 2) vasomotor phenomena, 3) elevated temperature, 4) hypertension, 5) postural tachycardia and hypotension, 6) B.M.R. of +20 or more, and 7) gastro-intestinal symptoms.

Two pharmacologic agents, histamine and Regitine, are used as aids to diagnosis. Intra-venous histamine .025-.05 mg. is used in patients with blood pressure of less than 170/100 mm. Hg. to stimulate catecholamine release from the tumour. Blood pressure is measured every 30 seconds for four minutes. A positive response is a systolic rise of greater than 60 mm. Hg. In patients with a blood pressure greater than 170/100 mm. Hg. 5 mg. Regitine is injected intra-venously and the blood pressure measured. This drug acts to block pressor amines thus reducing blood pressure. A positive response is an immediate drop of 35 mm. Hg. systolic and 25 mm. Hg. diastolic. Both tests are accompanied by some risk; severe hypertension with histamine and hypotensive shock with Regitine. They should be undertaken only under carefully controlled conditions.

VMA or catecholamine determinations on urine are the safest methods of diagnosing pheochromocytoma. Repeated measurements may be necessary. Intra-venous pyelography may show distortion of the kidney from the tumour.

Treatment of the condition is surgical removal of the tumour. The blood pressure during surgery may fluctuate wildly as catecholamines are released into the circulation. Post-operatively, however, most patients do well and 70% are permanently cured of their hypertension.

C. Coarctation

Coarctation of the aorta is an uncommon abnormality. Its importance is that it causes hypertension which may be very severe. Fortunately, coarctation is easily diagnosed and readily treated.

It is fascinating to contemplate why coarctation of the aorta should cause hypertension. It is thought by some investigators to be a simple mechanical block with compensatory hypertension to force blood through the collateral circulation around the obstruction. It has been shown, however, that when aortic constriction has been experimentally produced in dogs hypertension does not occur. Others believe that coarctation of the aorta causes renal ischemia, thereby stimulating release of renin from the kidneys.

There are two pathological types of coarctation, infantile and adult. The infantile form is characterized by diffuse involvement of the aortic isthmus with constriction proximal to the ductus arteriosus, a patent ductus and cyanosis. Other congenital anomalies are commonly present. The infantile type, as implied by the name, is usually fatal in infancy if untreated. In the adult type of coarctation the aortic constriction is more localized and is located at or beyond the ductus. The ductus is closed, there is no cyanosis and collaterals are well developed .Males are affected much more commonly (4:1) than females.

1) Diagnosis

Symptoms may be absent. Often, however, the patient will complain of headache, insomnia, tinnitus and epistaxis from the associated hypertension. Symptoms referable to the legs are also characteristic with weakness, coldness, numbness and cramps. Eventually the symptoms of cardiac failure may supervene.

The signs of coarctation are unmistakable. A disparity in the femoral and radial pulses is most important. The femoral pulse will be reduced or absent. Normally the femoral pulse occurs slightly before the radial but in coarctation there is a noticeable lag between the radial and femoral pulse. The blood pressure in the legs is much less than in the arms in coarctation although normally the reverse is true. Hypertension in the upper part of the body is the rule after age 10. Commonly a systolic murmur is heard over the base of the heart.

Roentgenographic examination is often helpful in adults. Chest X-rays should be examined for mild or moderate cardiomegaly, a small and indented aortic knob and anterior rib notching.

2) Treatment

Everyone with coarctation of the aorta should have it surgically corrected if their general condition permits it. The ideal age for correction is between 10 and 20

years. Surgery is not contra-indicated in other patients however, since the natural history of the disease is the development of severe hypertension with death before age 40.

Surgery consists of generous removal of all the involved aorta with direct anastomosis of the ends, or the insertion of a homograft or Teflon graft. The results of surgery are good. Post-operatively most patients show a marked drop in blood pressure although some require a few weeks or months for their blood pressure to fall. More than 80% of patients eventually become normotensive after surgery.

ACKNOWLEDGEMENT

I wish to thank Dr. R. J. Baird of the Toronto Western Hospital for the opportunity of working in the field of renal hypertension during the past summer.

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The Adrenal Steroids

PART I

J. C. Mueller 6T6

Biologically the corticosteroids are considered to be of two types, mineralocorticoids and glucocorticoids. The mineralocorticoids, of which aldosterone is the natural analogue, are active in salt and water metabolism. The glucocorticoids, of which hydrocortisone (cortisol) is the main natural active compound, are active in the maintenance of CHO stores in the body but also have anti-inflammatory, eosinopenic and pituitary-adrenal supressing actions. Although mineralocorticoid and glucocorticoid are terms denoting the physiological activity of the individual steroid, in actual fact, gluco- and mineralocorticoid activities overlap in most natural and synthetic adrenocortico steroids.

The adrenal steroids are all derived directly or indirectly in the body from cholesterol, although they may also be formed by other biosynthetic routes from simpler precursors such as acetate. The conversion of cholesterol to the hormones is governed, at least in part, by one of the adenohypophyseal hormones, namely ACTH. The biosynthesis of the adrenal steroids in the adrenal cortex is best illustrated by the following diagram.

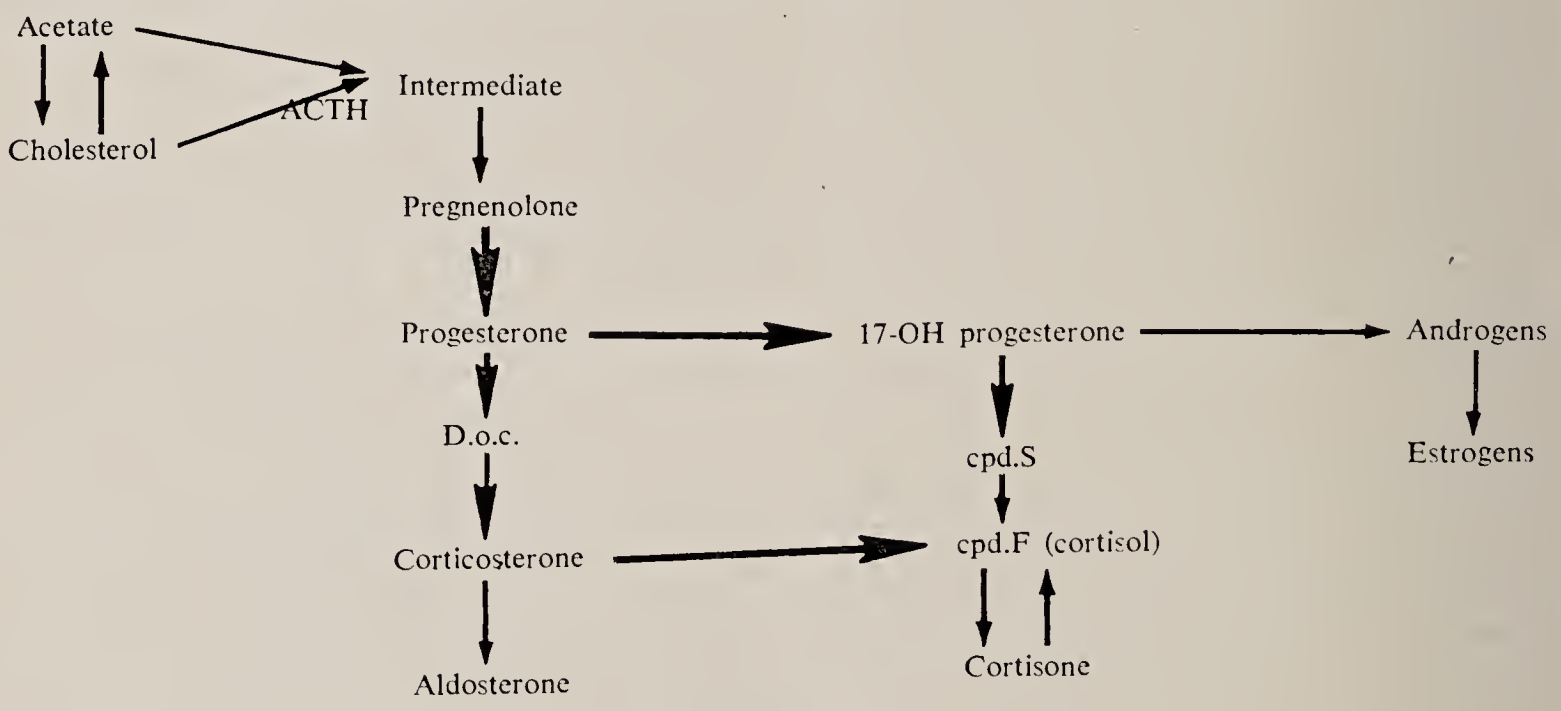

Figure 1

It is well known and generally accepted that cortisol is under the control of ACTH and that circulating cortisol exerts an inverse feedback effect on ACTH secretion. For more information on this mechanism the reader may consult any recognized medical text. The regulation of minerocorticoid secretion however poses more of a problem. The physiological stimuli and exact mechanism(s) of aldosterone secretion are still in doubt. The popular theory at the present seems to be the following. The most important stimulus to aldosterone production is a contraction of the extracellular fluid volume, independent of any change in the intracellular fluid volume, serum Na concentration or total body water, although the latter three factors are often altered simultaneously. The stimuli are carried by afferent neural signals to the hypothalamus. Here the neural signals stimulate the endocrine production of a humoral factor called by Farrell and his co-workers glomerulotrophin. Glomerulotrophin is carried in the blood and stimulates aldosterone production in the zona glomerulosa of the adrenal gland.

The concentration of cortisol in body fluids and tissues is a factor of the rate of continuous secretion and steady destruction of the hormone. The majority of the steroid is broken down by enzyme systems in the liver with a very small amount being destroyed by similar enzyme systems in the muscles, plasma and other tissues of the body. In the liver enzymes convert the corticosteroids to their relatively inactive tetrahydrocorticosteroid and 17-ketosteroid forms. The inactive forms are then conjugated in the liver with glucuronic and sulphuric acids. The conjugated inactive forms are highly water soluble thus rendering them able to be excreted readily in the urine. From renal clearance studies it has become evident that the conjugated steroids are excreted with an efficiency close to that of

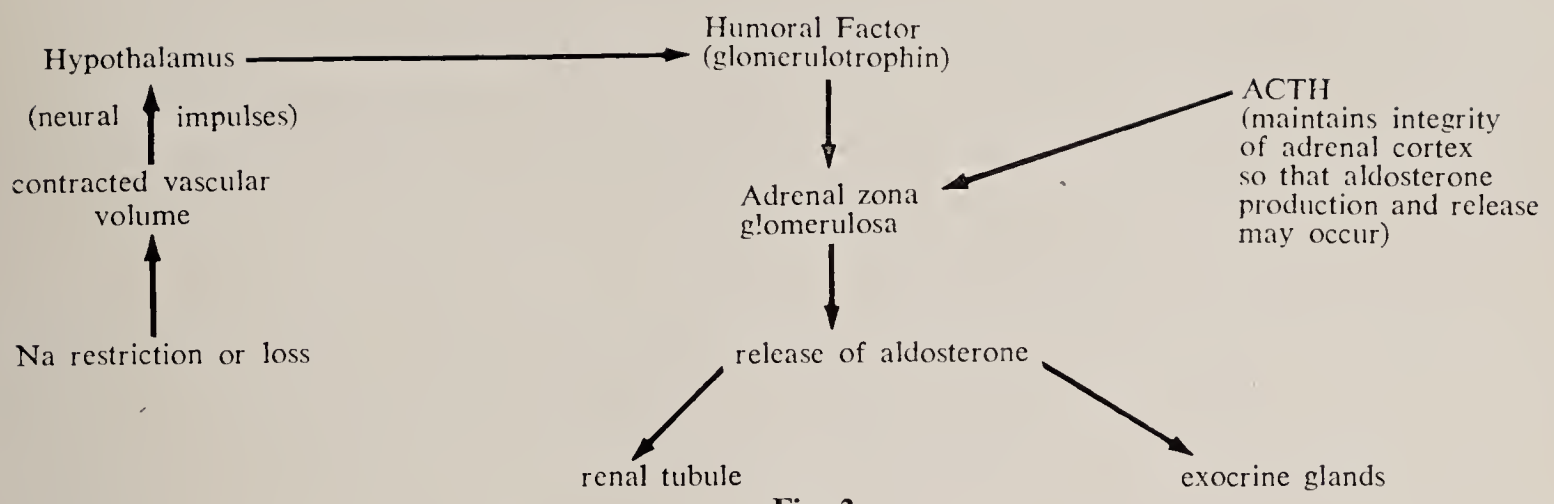

Fig. 2

creatinine and therefore that tubular reabsorption is negligible.

EFFECTS OF STEROIDS ON WATER AND ELECTROLYTE METABOLISM AND ON RENAL FUNCTION

The clearest results of the effects of the adrenal steroids are obtained by examining the consequences of states of deficiency and excess. From observation of the state of hypofunction of the adrenal cortex the following effects of steroids on electrolyte metabolism and renal function have been noted.

In adrenal insufficiency the serum electrolytes are altered such that there is a decrease in the serum concentration of Na^+, Cl^- and HCO_3^- accompanied by an increase in the serum level of K^+. These observations are in all probability intimately associated with the impaired renal conservation of Na^+, and the impaired capacity to excrete K^+, seen in Addison's disease. As a result of the loss of Na^+, Cl^-, and HCO_3^- in the urine there is a decrease in the serum water and a subsequent contraction of the plasma volume.

The moderate to severe cases of hypotension and orthostatic hypotension seen in Addison's disease were previously explained by the contraction of the plasma volume. Lately, however, there has been observed another phenomenon which is closely related to the hypotension. This is that in patients with Addison's disease there is a relative lack of response of the vessels to vasoconstrictors and to vasoconstrictor stimuli within the body. It seems that the combined effects of a contracted plasma volume and a decreased vascular reactivity to vasoconstritor stimuli play a large role in the hypotension of adrenocortical insufficiency.

Of the many other changes in bodily composition and function caused by Addison's disease, only the more important shall be mentioned. Firstly, it is paradoxical that Addisonian patients are unable to excrete an excess load of Na^+ at a normal rate even though they have an impaired renal conservation of Na^+. Secondly, they have an impaired ability to excrete a water load leaving them with a marked susceptibility to water intoxication. Thirdly, there is a decrease in the G.F.R. (glomerular filtration rate) and RBF (renal blood flow) independent of the loss of extracellular fluid and electrolyte. Finally, these patients have an impaired renal secretion of ammonia and hydrogen ion, accounting for a tendency toward extracellular acidosis and a decreased serum HCO_3^- level.

EFFECTS AND PROBABLE SITES OF ACTION OF THE ADRENAL STEROIDS ON THE KIDNEY NEPHRON

There is sufficient experimental evidence to confirm the fact that the steroids act primarily at three sites in the kidney nephron. The glucocorticoid action of the steroids takes place at sites one and four in the above diagram and the mineralocorticoid action at site three. In the proximal convoluted tubule and loop of Henle the steroids have yet to have been shown to have any effect.

In the renal circulation and glomerulus, i.e. site one, the glucocorticoids act to maintain the renal blood flow and glomerular filtration rate. The evidence for this stems from experiments showing that the glucocorticoids cause an increased GFR prior to any alteration in body fluids or solutes. Since glomerular filtration is a passive process, the increase is presumably secondary to an increased RBF. The glucocorticoids also act on the distal convoluted tubules and collecting tubules by preventing the back diffusion of water in the absence of circulating of ADH, thus allowing a normal water diuresis and a normal response to an excess water load.

The mineralocorticoid action is expressed mainly in the DCT and proximal collecting tubules. Here the effect of the mineralocorticoids is to enhance the reabsorption of Na^+ and the secretion of K^+, H^+ and ammonia. In practical terms, the mineralocorticoids support the cationic exchange mechanism of Na^+ for K^+, H^+ and ammonia, thus playing an integral part in the maintenance of acid-base as well as electrolyte balance. Further experiments have shown that the glucocorticoids (by virtue of their catabolic effects on tissue) may also influence the cationic exchange mechanism by releasing K^+ and making it available for excretion.

Aside from their renal actions on water, electrolytes and renal hemodynamics the steroids also demonstrate extrarenal effects. As was mentioned before, the glucocorticoids seem to be partially responsible for maintaining vascular tone and reactivity. Since it has been experimentally shown that adrenalectomized animals have relatively appropriate responses to the intraarterial administration of norepinephrine with respect to cardiac output, blood pressure and vascular response, it seems that the glucocorticoids do not act by modifying the cardio vascular response to the humoral action of norepinephrine but rather may directly affect the vasculature or some central area. The action of glucocorticoids in enhancing tissue breakdown throughout the body also affects electrolyte balance by the resultant K^+ liberation from the affected tissues. There is also inconclusive evidence pointing to the action of glucocrticoids in maintaining the intracellular-extracellular gradients of Na^+ and K^+.

In addition to their action on the kidney, the mineralocorticoids decrease the excretion of Na^+ and Cl^- and increase the excretion of K^+ from the sweat glands, saliva and gastrointestinal tract. They are also thought to maintain the concentration of extracellular Na^+ by mobilization from nonextracellular sites. As is the case with the glucocorticoids, there is inconclusive evidence that the mineralocorticoids also assist in the maintenance of the transcellular gradient of Na^+ and K^+.

Summary; of renal and extrarenal actions of steroids on water, electrolytes and renal hemodynamics.

A. Renal:

1. glucocorticoids:
   1. maintains normal level and reactivity of GFR and RBF.
   2. inhibits back diffusion of water in diluting segments in absence of ADH.
2. mineralocorticoids:
   1. enhances the distal tubular reabsorption of Na^+ and Cl^-.
   2. enhances the distal tubular secretion of K^+.
   3. enhances the distal tubular secretion of H^+ and diffusion of ammonia.

B. Extrarenal:

1. glucocorticoids:
   1. help sustains vascular tone and reactivity.
   2. enhances tissue breakdown and K^+ liberation.
   3. maintains intra- extracellular gradients of Na^+ and K^+.
2. mineralocorticoids:
   1. decreases excretion of Na^+ and Cl^- and increases excretion of K^+ from sweat glands, saliva and gastointestinal tract.
   2. maintains extracellular Na^+ by movement from nonextracellular sites.
   3. maintains intra- extracellular gradients of Na^+ and K^+.

EFFECTS OF STEROIDS ON THE METABOLISM OF CHO, FAT, AND PROTEIN

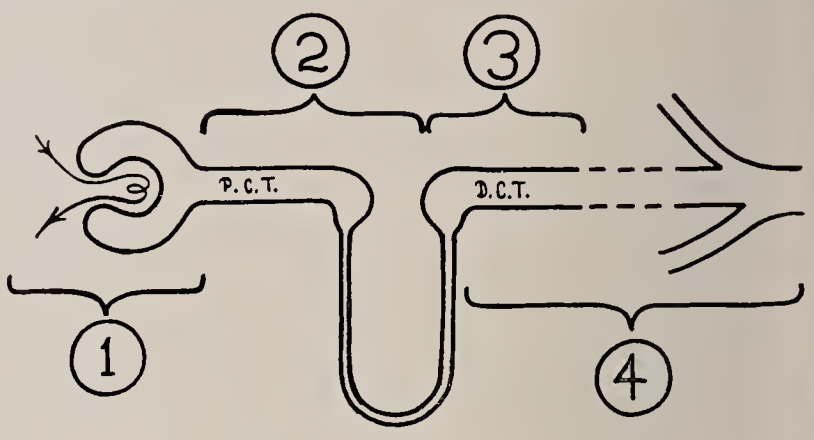

Fig. 3

The wasting and weakness of muscles, bone and skin, the elevated blood sugar and the increased deposition of fat in the trunk in patients receiving long term steroid therapy all attest to the actions of the steroids in the metabolism of CHO, fat and protein. In the normal human being however, cortisol secretion serves a homeostatic function, allowing the organism to return to a normal state "in response to changes or demands in the environment". In actual fact, under ideal conditions i.e. in the fully fed state with electrolytes maintained by dietary intake and with no exposure to bodily or psychic stress there is no deleterious effect of the absence of cortisol. Cortisol becomes essential to the maintenance of bodily homeostasis in the response to such changes in the environment as trauma, fasting, stress, etc.

To further elucidate the action of the steroids let us consider the bodily response to such an environmental change as fasting. In the absence of adequate dietary intake the blood sugar level falls below normal. To combat this the blood sugar is maintained by the release of glucose from liver glycogen, thus depleting the liver of its glycogen content. The liver glycogen is in turn replaced by the process of gluconeogenesis. That is, protein is mobilized from muscle, bone and skin and carried to the liver to be deaminated and converted to glycogen. In the absence of cortisol this process of gluconeogenesis proceeds at a very slow rate with the result that convulsions and death may occur from the developing hypoglycemia. A sufficient rate of protein catabolism and gluconeogenesis to maintain homeostasis requires the presence of cortisol. The events in the metabolic response to trauma and other bodily and psychic stresses are similar to that described above for fasting.

I have implied that the main action of the steroids is a catabolic one, i.e. an accelerated breakdown of body proteins to supply the amino acids necessary for gluconeogenesis. However, controversy is developing at the

present time as to whether the primary action of the hormone is catabolic or antianabolic. The antianabolic theory holds that steroids do not accelerate protein breakdown but rather decrease the rate of protein synthesis. The liver simply responds by receiving the excess amino acids not used for protein synthesis and handling them by storage as glycogen and conversion to serum proteins and urea. It remains to be elucidated which, if either, is the primary action of the hormone.

PART II

A. G. Kelly 6T6

MAJOR CLINICAL USES OF STEROIDS

Every physician must ponder seriously his decision to use steroids. It cannot be too strongly stressed that steroids cause a profound change in the endogenous steroid metabolism of the patient. One must remember that the patient is dependent on this metabolism for meeting the stresses and strains of life.

The criteria for the use of steroids, the contraindications, the risk, and the dosage vary from disease to disease. No aboslute rules can be made for steroid treatment but, patterns can be presented and may be used as rough guides for the individual treatment of patients.

COMPLICATIONS OF PROLONGED STEROID USE

The following complications may occur in any disease treated by prolonged steroid therapy.

1. Cushingoid feautres such as a moon face, trunkal obesity, and striae of the skin, may develop.

2. Peptic ulcer and gastointestinal bleeding.

There is an increased incidence of peptic ulcer in patients who have previously had no symptoms. Those patients having a history of peptic ulcer, usually have a recurrence or an aggrevation of symptoms.

The presence of anemia in a patient on steroid therapy suggests gastrointestinal bleeding.

3. Osteoporosis

Osteoporosis occurs to some degree in all patients who are on steroid treatment. Postmenopausal women and elderly men are predisposed to earlier changes. The first changes are noted in the vertebral bodies. Patients complain of pain in the bones, especially the back. They may present with a fracture of the vertebral body.

4. Infections

In the absence of specific antibotic therapy, an infection may spread rapidly if the patient is on steroids. Tuberculosis may be reactivated during therapy. Patients should have a chest film prior to treatment and periodically during the course of treatment.

5. Personality changes

Minor changes such as euphoria, insomnia or excessive activity occur in some cases. Major psychotic episodes such as manic-depressive reactions, schizophrenia or acute toxic psychosis may occur and do necessitate cessation of therapy.

6. Systemic Hypertension

Hypertension may occur in as high as five percent of the patients on prednisone. If the diastolic pressure is greater then 100 mm. of mercury, the steroids should be decreased.

RHEUMATOID ARTHRITIS

Indications

The specific indications for steroids in rheumatoid arthritis are not clearly defined. Steroids should never be given as the initial treatment and should only be considered after a trial on more conservative therapy. When steroids are considered they should only be one facet of a general treatment program which includes physiotherapy, rest, A.S.A., and restricted use of damaged or inflamed joints. These drugs should only be considered after a careful analysis of the contraindications.

Specific Indications

1. Unmanageable, rapidly progressive systemic or articular disease.

2. Unbearable pain requiring narcotics.

Risks

These patients are subject to all the complications of prolonged steroid therapy as outlined previously. In addition patients with rheumatoid arthritis who are on long-term therapy may develop a mesenchymal response characterized by cyclic swings of mood, aching, tiredness, and emotional instability during the course of a day. The symptoms are usually relieved by a short rest. The pathology is usually that of diffuse polyarteritis nodosa but may also be that of disseminated lupus erythematosus or of polymyositis. This response is reversable if detected early. It is not usually found if the patient is kept on physiologic dosages of steroids.

CONTRAINDICATIONS

(a) Absolute
   1. active infection such as tuberculosis
   2. severe diabetes
   3. active peptic ulcer

4. severe emotional instability or psychosis
5. marked renal insufficiency
6. severe cardiovascular disease
7. cushings syndrome

(b) Relative

1. arrested tuberculosis
2. mild diabetes
3. generalized osteoporosis
4. thrombo-embolic phenomena
5. history of peptic ulcer
6. convulsive disorders
7. pregnancy

MODES OF ADMINISTRATION

1. Intraarticular
2. Small suppressive dose for a long period

INTRAARTICULAR

Indications

This method should be used if only a few joints are involved or if the systemic reaction is suppressed but a few joints lag behind. It may also be given for temporary relief of pain in an acutely painful joint.

Risk

The main risk is that of mechanical damage incurred by excess use of a joint which is suddenly free from pain. There is a very slight risk of infection being introduced into the joint.

Dose

Hydrocortisone acetate, 10-50 mg. is commonly used. Equivalent doses of prednisolone acetate or prednisolone t-butyl acetate may also be used. The effect usually lasts 8-12 days after each injection.

Cause of Ineffectiveness

1. poor systemic suppression
2. misuse of joint
3. local infection

SMALL DOSES FOR LONG-TERM TREATMENT

The dosage is based on age, sex and tolerance. The steroid chosen depends on personal preference. The maximum maintenance dose of prednisone for men is 7.5 mg., for women, 6 mg. and for post menopausal women, 4.5 mg. per day.

The total dose is divided as equally as possible into three doses and given every eight hours.

During an acute flare-up prednisone 20-25 mg. per day in divided doses may be given. It is then slowly withdrawn to the original dose. For minor flare-ups, conservative therapy alone, should be used. Attempts should be made to gradually discontinue all steroids.

During long-term therapy, prophylactic antacids should be given to counteract the effects of steroids and of aspirin on the gastrointestenal tract.

Effectiveness of Drug

The patient should experience less jelling and subjective stiffness. He should sleep well and his appetite should return to normal. The synovitis should subside slowly for satisfactory progress.

RHEUMATIC FEVER

Indications

All patients should be treated with steroids unless there are specific contraindications. The best results are obtained if they are given within three weeks of the beginning of the illness.

Specific Risks in Treating Children

1. Development of hepatomegaly
2. Development of an intercurrent infection

If varicella occurs the drug should be stopped. A severe form of varicella with a high mortality rate may occur if the patient is on steroids.

Dose

Some advise an initial dose of prednisoné of 60 mg. per day, (1.3 mg. per pound body weight). This dose is maintained until all evidence of disease activity has disappeared, (usually 2-3 weeks). The drug is then gradually withdrawn over a period of 5-6 weeks. If the disease is reactivated, the dose is increased. Others advise immediate withdrawal over a period of two weeks after the same initial dose.

Additional Drug Treatment

1. aspirin ½ gr. per lb. daily for three months
2. penicillin 1,200,000 units benzathine I.M. stat and repeat on seventh and fourteenth days. Continue once per month for a year. Continue oral penicillin 200,000 units once or twice a day until age twenty five.

Effectiveness of the Drug

Steroids have been found to decrease the heart signs found one to three years following the first attack. Dorfman et al found in a series of 128 patients, that of those treated with hydrocortisone alone or with A.S.A., 16% of those with heart murmurs initially had residual heart disease. However in those with heart murmurs initially who were treated with A.S.A. alone or with no antirheumatic drugs, 40% still had residual heart disease.

Other investigators feel however that in long term follow up there is no conclusive evidence that steroids do reduce the number of patients developing heart disease. Until this problem is resolved the physician should continue to treat acute rheumatic fever with steroids.

ULCERATIVE COLITIS

Indications

1. Failure of conservative medical management
2. Seriously ill patient with sufficient incapacity from the disease process to warrant the risks of corticosteroid therapy.

Contraindications

1. The existence of colitis so severe that immediate surgical intervention is necessary e.g. perforation of the colon with generalized peritonitits or exsanguinating haemorrhage.

2. Relative contraindications may be the presence of a peptic ulcer or a history of tuberculosis. However these problems can be treated while the patient is on steroids.

Dose

Prednisone, 60 mg. per os (or its equivalent) is given daily in divided doses. If there is no response in three days, aqueous A.C.T.H. may be given in the amount of 30 units I.M. four times a day. If there is no response after three days, A.C.T.H. may be given as a continuous I.V. infusion at the rate of 40 units per day. If still no effect after two to three days, then discontinue all steroids.

The dose is reduced as soon as the patient is afebrile, having six or less stools a day and is eating well. The reduction program is continued until an exacerbation occurs or until the patient may be taken completely off the hormone.

TOPICAL TREATMENT

Indications

In mild cases, topical treatment alone should be used. In moderate and severe cases, both systemic and topical treatment may be advisable.

This method of administration has a real advantage because it eliminates the possibility of systemic side effects.

Dose

Hydrocortisone hemisuccinate, a water soluble corticosteroid, is used. It is administered by rectal drip, 100 mg. in 100 c.c. of saline, over a thirty minute period, two or three times a day.

This regimen is continued until the symptoms are brought under control. After this, only a nightly enema is given. Gradually this too is withdrawn after the patient has had at least a two week remission. If the diarrhea is so severe that an enema cannot be given, codeine or anticholinergic drugs may be used to slow down the intestinal motility. Kaon, 15 c.c., should be given daily to compensate for the potassium that is lost due to diarrhea.

Effectiveness of drug

1. Clinical improvement i.e. diarrhea and temperature decreases
2. Colonic lesions heal but this takes several weeks
3. Decrease in systemic upsets, improvement in appetite and well-being.

Steroid therapy has no place in the chronic stages of ulcerative colitis. However, steroids may be used for allergic skin lesions and for arthritis which may accompany ulcerative colitis.

NEPHROTIC SYNDROME

Indications

Steroids have their greatest effectiveness in the nephrotic syndrome due to lipoid nephrosis and membranous glomerulonephritis. However, they should be tried in nephrotic syndrome due to other primary renal disease and probably in disseminated lupus erythematosus involving the kidney.

Principles of treatment

1. Corticosteroids should be given in large dosage as soon as the diagnosis is made.

2. The preparation depends on personal preference.

3. Initial treatment should be continued for a long time, long enough, if possible to return the patient to a relatively normal state with regard to all the available measurements.

4. After initial treatment, some long-term plan should be made for either retreatment or continued treatment. Some give steroids continually, gradually reducing the dose. Others reduce the dose fairly rapidly after signs of a remission and then wait for signs of a relapse.

5. The response to treatment should be clearly defined as follows:

(i) Group 4 — complete remission with the proteinuria less then 90 mg. per 24 hours.
(ii) Group 3 — a partial response. There is a decreased proteinuria and increased serum albumen with loss of nephrotic signs and symptoms.
(iii) Group 2 — a quantitative lessening of proteinuria without a significant rise in the serum albumen, but with loss of edema.
(iv) Group 1 — Control of edema only.
(v) Group O — A failure to improve significantly.

6. For patients who do not have a complete remission, some form of long term therapy should be instituted.

Treatment regimen

In order to lessen the side effects, one of the following plans should be used.

1. Twice the normal daily dose is given for three consecutive days each week.

2. Twice the normal dose may be given every other day.

Duration of treatment

Initial: At least five weeks continuous treatment should be given. If a remission occurs, treatment should be continued at least for two weeks more.

Relapse: If a relapse occurs treatment should probably be continued for at least one year.

Risks

The risks of prolonged steroid therapy are similar to those for other diseases.

Effectiveness

Although some spontaneous remissions do occur, the effectiveness is based on the response graded from Group 4 to Group 0.

BRONCHIAL ASTHMA

Indications

1. An acute asthmatic attack which does not respond to bronchodilators, hydration, expectorants and oxygen in one or two days.

2. Asthmatic patients requiring surgery, especially thoracotomy should receive steroids before the operation.

3. Prolonged steroid therapy may be necessary to prevent severe chronic airway obstruction and resultant permanent emphysema.

Risks

Those complications related to prolonged steroid therapy may occur.

Choice of Steroid and Dosage

Prednisone, 10 mg. four times a day is usually sufficient, but this may be increased ot 60-80 mg. daily if necessary. This dosage should be gradually reduced. If a relapse occurs one should return to the original dosage, and again attempt slow withdrawal of the drug.

In severe refractory cases, A.C.T.H. by I.V. or I.M. may be used. A.C.T.H., 40 units in 1000 c.c. of glucose and water, is given by slow I.V. drip over a period of 12 hours. A.C.T.H. is then discontinued for 12 hours and the patient is observed. This regimen may be repeated if necessary.

In refractory cases the patient should be maintained on the lowest dosage which will control the disease. Some symptoms such as mild shortness of breath and rales in the chest may persist. The daily dosage of prednisone should not exceed 7.5 - 12.5 mg. Once a year the steroids should be withdrawn to see if the patient can get along without them.

Topical steroids may be used instead of systemic therapy. There is little danger of side effects or complications with topical administration. Dexamethasone, two inhalations four times a day, will give a total daily dose of 0.75 mg.

Criteria for Improvement

1. Patient feels better
2. Decreased sibulant rales
3. Decreased production of sputum
4. Improved pulmonary function tests

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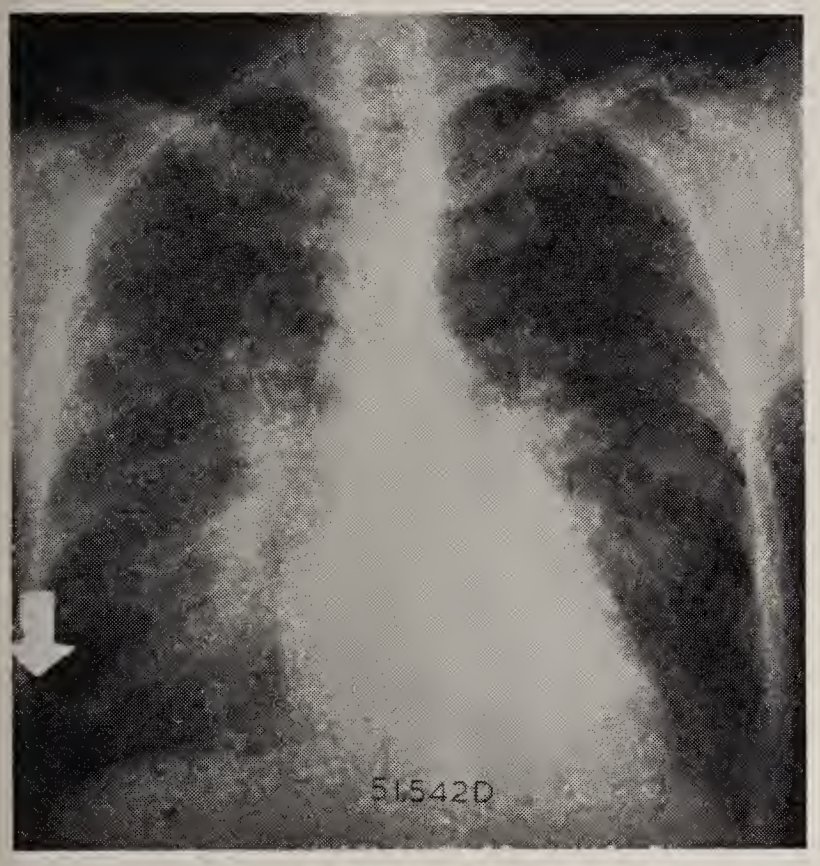
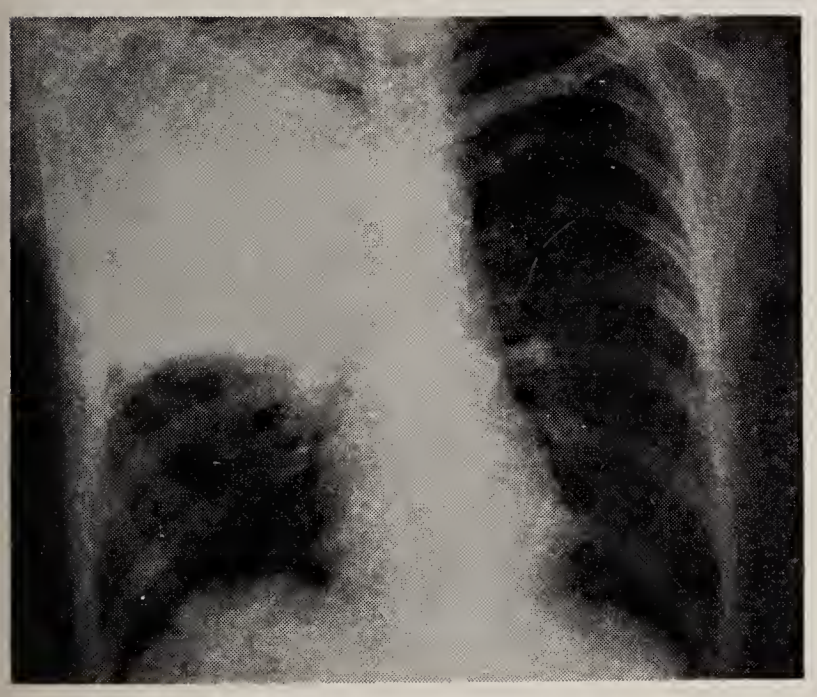
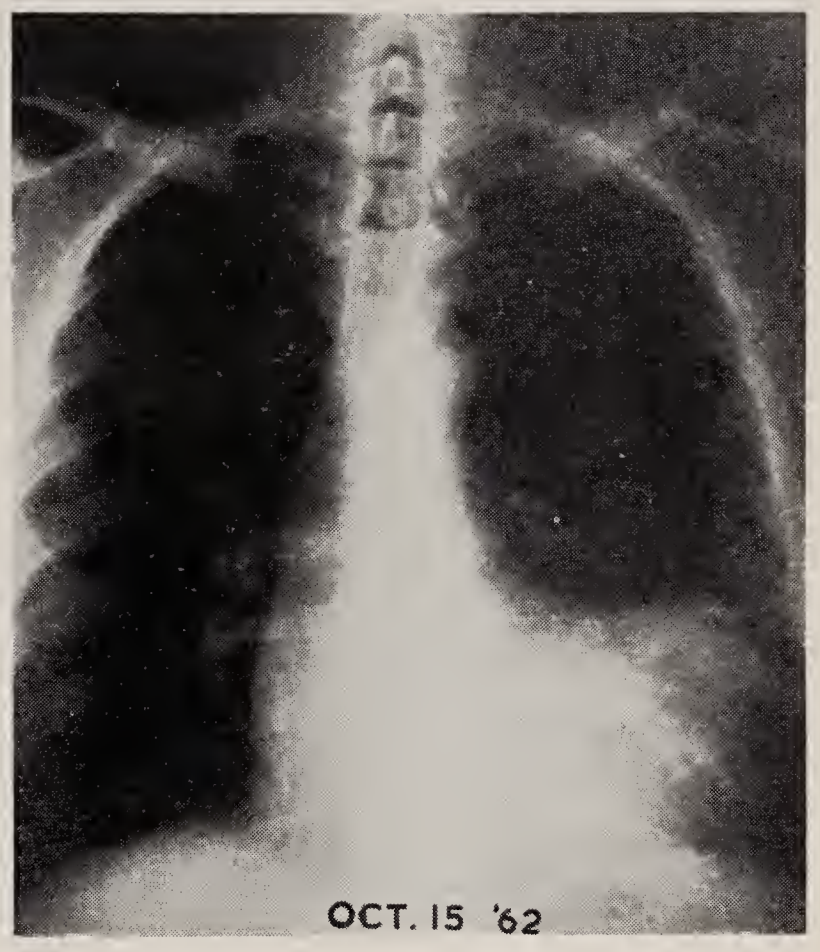


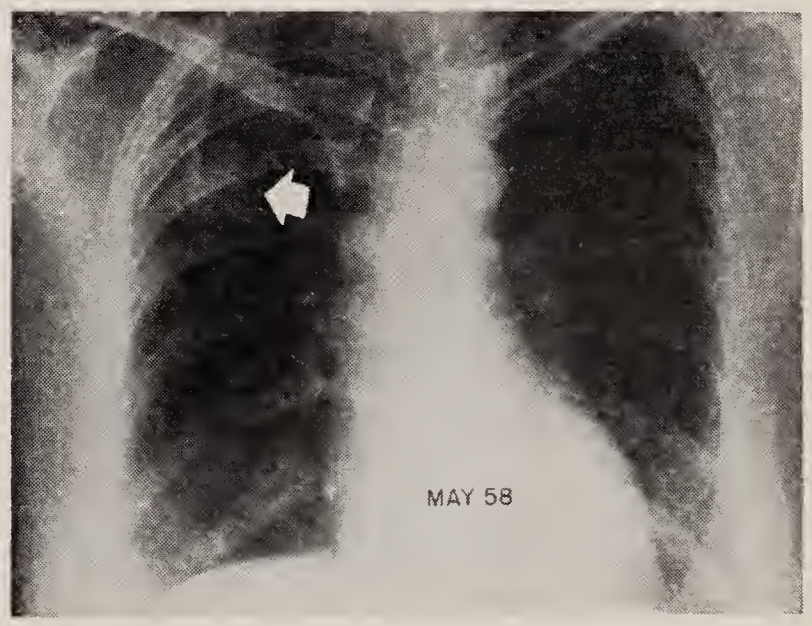
1. 39 year old male patient has had increasing palpitation and fatiguability for three years.
   a) What is the name and what are the causes of the horizontal line shadows (arrow).
   b) Diagnosis? Reasons?



2. a) What is the name and cause of this appearance?
   b) Gram positive diplococci were isolated from the sputum. Diagnosis?
   c) Outline the typical onset.
   d) List the typical signs.
   e) Usual course and possible complications?



3. a) Diagnosis?
   b) What acute event usually precedes the development of this lesion?
   c) List the typcial story of chest pain experienced when this acute event occurs.
   d) Prognosis?



4. a) What is the name commonly given to the lesion in the right upper lobe?
   b) List the possible causes of this lesion.
   c) Diagnosis?

Answers on page 124

Haemolytic Disease Of The Newborn

Gary J. Douglas 6T6

INTRODUCTION

The term "Haemolytic Disease of the Newborn" (HDN) is given to classify a broad group of haemolytic processes seen in the newborn infant. It was introduced to replace the narrow and ambiguous term "Erythroblastosis Fetalis". By far the most common cause of haemolysis in the newborn is an incompatability between the red cells of the mother and those of the offspring. Differences in ABO grouping cause haemolytic disease almost twice as frequently as differences in Rh factor or other blood group systems. ABO incompatability is often missed, however, because it rarely is suspected before delivery and the clinical picture after delivery is usually mild. Other rare diseases such as congenital spherocytosis, toxoplasmosis, congenital lues and sepsis can cause haemolysis and are included in the term, but will not be considered here.

The term is not ideal, for much of the haemolysis and subsequent damage is done in-utero, before the newborn period. After delivery, the condition, unless irreversible, usually improves. Furthermore many cases of haemolytic disease result in death in-utero with no "newborn" period possible. Perhaps these conditions would be more properly classified under "Congenital Haemolytic Disease".

This paper will be restricted to a discussion of haemolytic disease caused by Rh incompatibility.

A. Requirements

1. An Rh negative mother with an Rh positive foetus.

In approximately 5% of such pregnancies, the disease will occur. This situation results from the union of an Rh positive man with an Rh negative woman. The genotype of the male is important. If he is homozygous as nearly one half are, then all the offspring will be Rh positive. If he is heterozygous, then in each pregnancy there will be a 50% chance of the baby being Rh positive.

2. Introduction of the antigen on the red cell surface to the maternal circulation. Leakage of foetal red cells across the placenta can be detected at the end of the first trimester and increases thereafter until the time of delivery. This suggests a gradual deterioration in the placental barrier with time.

3. Maternal response with the production of anti-Rh antibodies.

Two varieties are sometimes produced in the same patient. One causes agglutination of red cells suspended in saline solution. This is called the "saline" or "direct agglutinating" antibody. The other causes agglutination of red cells suspended in albumin or other protein media but is ineffective with red cells suspended in saline. This is referred to as the "incomplete antibody".

4. Transfer of the antibody across the placenta to the foetal circulation. Only the incomplete antibody is capable of crossing the placenta. It would appear that the direct agglutinating antibody is unable to reach the foetal circulation and, therefore, does not contribute to the disease.

5. Combination of antigen and antibody without complement followed by destruction of affected foetal red cells by the reticulo-endothelial system. Intravascular haemolysis with hemaglobinemia rarely if ever occurs.

B. Results

The degree of foetal involvement from the above process ranges from very mild to very severe.

Before delivery—In mild cases there is little or no change in the foetus. Compensation for red cell haemolysis is achieved with an increase in red cell production. At most, a slight level of anaemia is present. In severe cases, compensation, in spite of massive extramedullary hematopoiesis, is impossible. Gross anaemia leads to congestive heart failure, foetal hydrops, and death in-utero.

After delivery—Here again, mild cases may show only slight anaemia or jaundice and thereby escape detection. The more serious forms develop progressive anaemia, and because of an immature liver, also a rapidly rising level of indirect serum bilirubin. If this is left untreated, kernicteris may result, either killing the infant, or leaving him with permanent brain damage.

C. Diagnosis and Assessment

1. Maternal Antibody Titre.

The presence of anti-Rh antibodies in a woman who, prior to her pregnancy had none, is diagnostic of the disease. Also the antibody titre in this case is a fair estimate of the severity of the disease. A low titre (¼) usually indicates mild affliction and a high titre (1/64) usually indicates severe affliction. In subsequent pregnancies, after Rh-immunization has occurred, the diag-

nosis cannot be made with certainty. In suspected cases the titres no longer correlate with the degree of involvement. Stillborn infants may be born to mothers with low titres and normal infants to mothers with high titres.

2. Past Obstetrical History.

This is also a useful aid in predicting the outcome of a pregnancy. In a woman with several past pregnancies, a pattern of increasing severity can sometimes be seen. For instance, she may have had a normal infant, followed by one requiring several exchange transfusions, followed by a stillbirth. In this instance there is less than a 10% chance of her delivering a normal Rh positive child. Unfortunately, this pattern is not constant. When present, however, a poor past obstetrical record is a strong indication for careful management and vigorous treatment.

3. Condition of the Foetus

By following foetal heart rate and spontaneous foetal movement one can often judge when the foetal condition is deteriorating. The problem is that once the disease has reached this stage, the chance of saving the foetus is much reduced. Hence an earlier, more accurate means of diagnosis and assessing an Rh-affected infant is required.

4. Direct Anti-Globulin Test (Coombs Test)

Coombs serum is a concentrate of anti-human globulin antibody prepared in rabbits by immunization with human serum. It is added to freshly washed foetal red cells taken from the cord vein immediately after delivery. After centrifugation, a positive test is indicated by the presence of red cell agglutination. The test is positive in haemolytic disease due to blood group incompatibility because the infant's red cells are coated with maternal antibody. This antibody is a protein and as such acts as an antigen for the prepared Coombs serum. The reaction of antigen (maternal gamma-globulin) and antibody (rabbit anti-human globulin) results in agglutination of the red cells. This test is very useful in diagnosing the condition but has the drawback of not being applicable until after the time of delivery.

5. Amniocentesis[5 7 8 9 12]

Spectral examination of amniotic fluid provides the diagnostic tool so long lacking in Rh disease.

X-ray of maternal abdomen 24 hours after intra-amniotic injection of Hyopaque showing dye concentrated within the foetal intestine. The marker indicates the path of the needle used for transfusion in-utero.

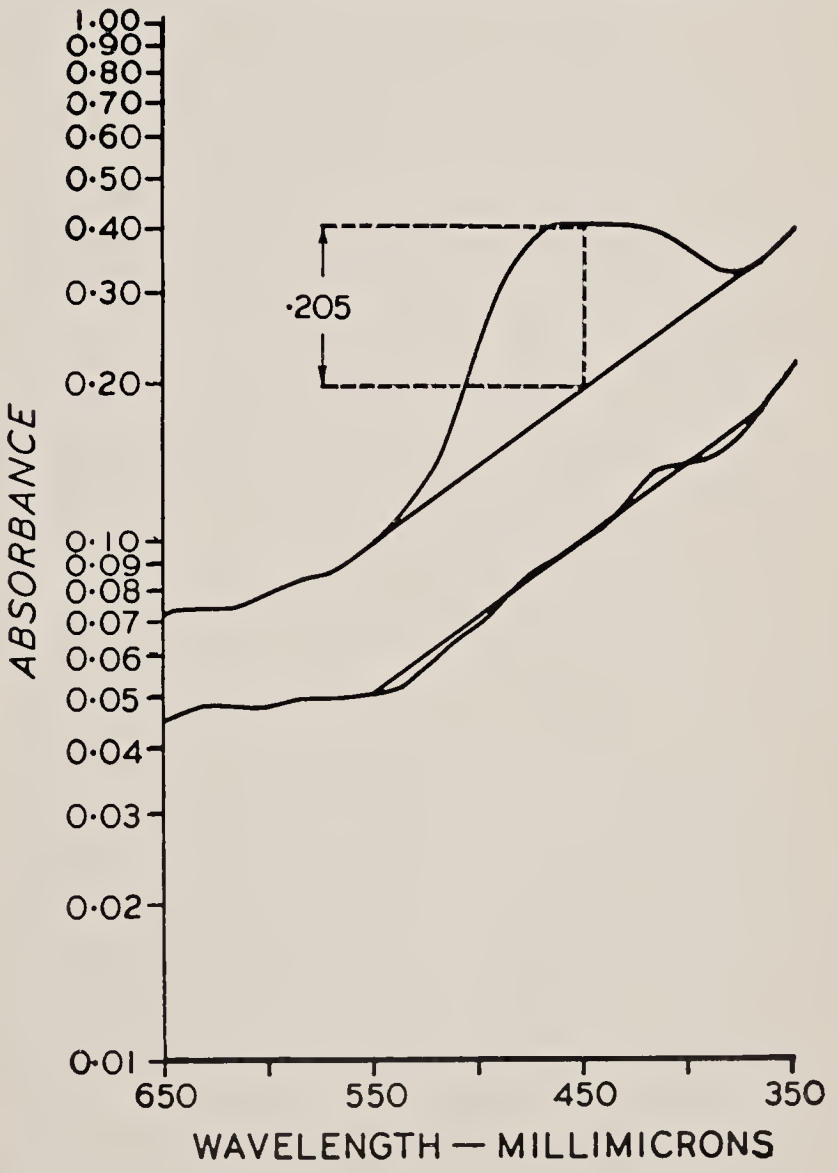


Figure 1. Spectrophotometric tracings. Lower tracing obtained on amniotic fluid from a normal foetus. Upper tracing obtained on amniotic fluid that was associated with a moderately affected baby. The size of the peak is measured (.205) and this value is plotted on the severity grading chart. (see Figure II).

(a) History—Bevis in 1950 was the first to analyze amniotic fluid with a spectrophotometer. Later in 1957, Walker added to the experimental usefulness of this technique, but it was left for Liley in 1961 to make the procedure practical for a hospital setting.

(b) Procedure—Amniotic taps are done on an out-patient basis under local anaesthetic. A 4-inch, No. 20 gauge spinal or Tuohy needle is introduced through the mother's abdomen and continued to and through her uterus into the amniotic sac. Ten cc. of fluid are aspirated, after which the needle is removed, with no interruption of the pregnancy.

(c) Examination and Analysis — The amnotic fluid is now examined with a spectrophotometer and the absorption curve between 350 and 650 mu plotted on semi-log paper. This device measures the absorption of a band of light passed through a tube of amniotic fluid. The spectrophotometer is desgned so that the absorption of light is seen as a positive deflection instead of the actual negative deflection that occurs. Normal fluid is clear or straw coloured and because it contains no pigment, no light is absorbed by it. Therefore in a normal pregnancy at term the absorption curve will show a relatively straight line between 365 and 550 mu. A small peak at 450 mu is seen early in the third trimester and is believed to be due to the presence of bilirubin. It reaches its maximum height between the 28th and 33rd weeks and as the pregnancy approaches term, it declines in size. The value for the peak is estimated by measuring the perpendicular distance from the tip of the peak to a base line drawn between the points 365 and 550 mu. (see Figure I).

In an affected foetus, red cell destruction occurs at a much faster rate than normal. This results in a markedly increased turnover of the breakdown product bilirubin. This pigment finds its way to the amniotic fluid and stains it yellow. The mechanisms for its excretion into the amniotic sac and eventual elimination are at present unknown. The presence of bilirubin or bilirubinoid products in the amniotic fluid changes the absorption curve. Light is absorbed at the 450 mu wave length in direct proportion to the concentration of pigment present. This in turn varies directly as the severity of foetal haemolysis. The size of the pigment peak in an affected pregnancy is much larger than normal during the 28th to 33rd week and thereafter stays the same large size or continues to increase even further. (see Figure I).

A peak at 415 mu is sometimes present and is thought by some to be a contaminant resulting from previous haemorrhagic taps.

Because both the size and progress of the 450 mu peak are used prognostically, repeated amniocentesis are more useful than a single amnotic tap. As a rule, all patients found to have anti-Rh antibodies during the initial screening at 12 to 16 weeks, undergo two or more amniocenteses. The first is usually done at 28 weeks (earlier if the past obstetrical history indicates so) and the second, three weeks later.

It is now customary to divide the absorption curves of amniotic fluid into three categories. (see Figure II) This enables the obstetrician to predict what the natural outcome for the baby would be without prenatal treatment, and thereby plan the best method and timing of treatment to improve on this.

(i) Curves in the lowest zone.

At birth these babies will be found to be either not affected or very mildly so—no distinction is possible from amniotic fluid investigation. In this zone the peaks usually decline as the foetus matures. Pregnancies here can be carried to term without danger.

(ii) Curves in the middle zone.

The interpretation of curves in this zone is complicated—three possibilities exist. This is why serial examinations are necessary. Some curves will shrink with time, indicating descent into the lowest zone, i.e., mild affliction. Others will remain stable in the mid-zone, indicating moderate involvement requiring early induction of labour and careful post-natal management.

Finally some curves will be seen to increase, with a rapid progression towards the upper zone, indicating a rapid decline in the foetal condition.

(iii) Curves in the upper zone.

These babies are severely affected and close to death. They require immediate and vigorous management in utero and post-natally to provide even a chance of survival.

(d) Complications of amniocentesis.

Complications are rare—a few cases of infection, haemorrhage, spontaneous delivery and foetal exsanguination have been reported. Most arguments against the procedure are theoretical and have yet to be seen clinically. Some critics feel there is a risk of increasing the severity of the disease in future pregnancies by releasing more foetal red cells into the maternal circulation with a traumatic tap.

D. Management

Up until a few years ago, nothing could be done to alter the natural history of the disease. Many pregnancies ended prematurely or carried to term with delivery of a stillborn or hydropic baby. Some infants survived delivery but soon became severely jaundiced and developed kernicteris.

1. Exchange Transfusion[6 13]

This was the first major contribution to the management of this disease, introduced by Wallerstein in the mid 1940's. With repeated exchange transfusions, the high levels of toxic indirect bilirubin which lead to

the development of kernicteris (greater than 20 mg.%), can be controlled and the infant saved. The transfusions also raise the haemoglobin level, which in many infants is dangerously low.

In this procedure, the umbilical vein is cannulated and 20 cc. of blood removed followed by the injection of 20 cc. of fresh Rh negative donor blood into the same vein. This is repeated until 500 cc. of blood have been exchanged, representing about 85% of the infant's total blood volume. As a result, serum bilirubin levels usually drop to about 1/3 of their original level. However because large amounts of bilirubin are also present bound to the body tissues, and because equilibration between tissues and plasma occurs, the final plasma level rises a few hours later, but usually not to the original high level. Transfusions are begun as early and repeated as often as necessary until safe stable levels of bilirubin are achieved.

Actually several factors are responsible for eliminating the danger of kernicteris. The most important of these is the maturation of the liver. When this occurs, the infant then becomes able to congugate indirect bilirubin to direct bilirubin and then excrete it through the G.I. and renal systems. The exchange transfusion merely functions as a dialyser of bilirubin until hepatic maturation occurs. An infant born prematurely will require more times for his liver to function normally than will an infant born at 40 weeks gestation. It follows then that these prematurely-delivered infants are more prone to develop kernicteris than full-term infants, and will require more and earlier exchange transfusions. Another factor of importance is the gradual catabolism of all body proteins which is constantly occurring in the body. Thus the offending antibodies are slowly eliminated from the circulation, once their source of supply, the maternal circulation has been removed. The half-life of the anti-Rh antibody is about thirty days.

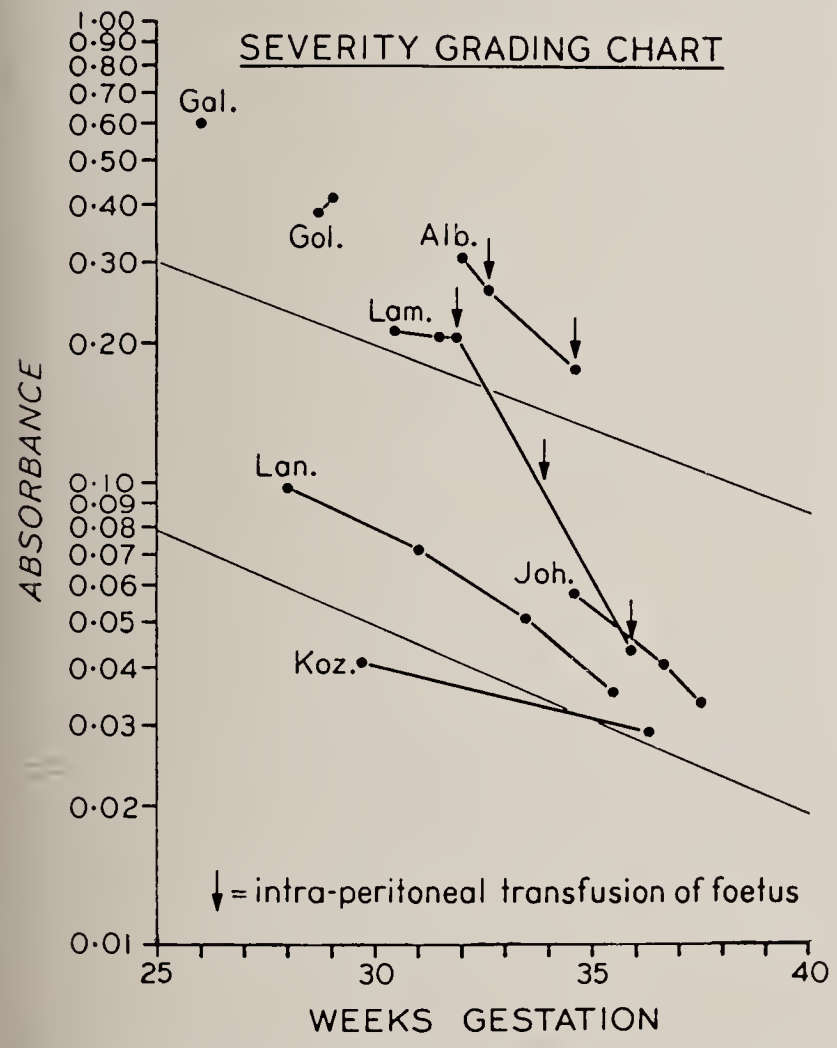


Figure 2. Severity Grading Chart. Serial values of the 450 mu absorption peak are plotted, showing the three zones of severity. The beneficial effect of transfusion inutero is apparent. Gal. and Gol. were associated with babies that subsequently died. Alb. and Lam. were obtained on fluids before and after intrauterine transfusion. Koz. was associated with a moderately affected baby, as were Lan. and Joh.

2. Early Induction of Labour[3]

By delivering a severly affected foetus at 37 weeks rather than 40 weeks, treatment by exchange transfusion can be started earlier. Many infants are saved this way, who might die if left until natural delivery. The benefits of early treatment must be balanced against the risks of immaturity in each case. As a rule, the cord is clamped early to keep the volume of blood in the newborn at a minimum. The more blood present, the more blood destroyed and the higher the levels of bilirubin.

3. Transfusion In Utero[2 4 10 11]

(a) History

In 1963, Liley, the same New Zealand obstetrician who developed amniocentesis into a practical diagnostic technique, was the first to successfully transfuse a foetus in-utero. Up until that time, there had been widespread fear of tampering with the foetus for fear of infection, haemorrhage or abortion. Liley's magnificant pioneer work quickly disproved all of this and supplied the first effective method of managing haemolytic disease in-utero. By transfusing the severely afflicted foetus, Liley was able to prevent the anaemia from developing which, in the past, had often lead to heart failure, hydrops and death before the time of delivery.

(b) Procedure (see photograph)

Amniocentesis is performed and 30 cc. of Hyopaque injected into the amniotic sac. The next day the foetus can be seen under the image intensifier and because of continuous swallowing of amniotic fluid, the G.I. tract can be outlined. A tuohy needle is directed into the amniotic sac and continued on until the foetal abdomen is pierced. The tip of the needle now lies within the foetal peritoneal cavity. Group O, Rh-negative donor cells, warmed and tightly packed, are slowly injected into the peritoneal cavity. The amount injected varies with the maturity of the foetus—usually between 50 and 150 cc. The Tuohy needle is now removed and the procedure is finished. Intra-uterine transfusion can be attempted as early as 24 weeks gestation and repeated as often as necessary (usually two or three

times). The results are gratifying — 30% or more of pregnancies originally considered as hopeless are now brought to term,—and the infants delivered in good condition. Some births have been reported where 100% of the cord blood is derived from the transfusion -in-utero (i.e. no foetal red cells are present).

Once these infants have been delivered they can be managed with further exchange transfusions in the usual manner.

(c) Theory

It has been known for some time that red cells placed in the peritoneal cavity will find their way into the general circulation. It has recently been shown that this is accomplished via the lymphatic drainage system. The transfused red cells are picked up by tiny peritoneal lymph vessels and carried to the cysterna chyli and thoracic duct before being released into the subclavian vein. In a hydropic foetus with ascites, this transfer is impeded and less than 50% of the transfused cells are successful in reaching the general circulation. Therefore it is important that in-utero transfusions be attempted before the foetus has become hydropic.

Because the foetal blood group is not known, group O, Rh-negative cells are used as donor cells. These foetuses are small and can only accept a small volume of fluid injected intraperitoneally. Therefore the cells are tightly packed so that little citrate or donor plasma are included in the transfusion. The same principle applies here, as with exchange transfusions, in the use of Rh-negative cells. Foetal red cells, being Rh-positive, are destroyed soon after their production, in the presence of anti-Rh antibodies. Their average survival time is 10 days compared to 120 days for normal red cells. The transfused cells being group O are still compatible with the foetal immunological system, but being Rh-negative are unaffected by the anti-Rh antibodies. Thus the donor cells with their normal survival time are able to carry out the usual functions of red cells, which the foetal cells, fewer in number and with their much shortened survival time, have been unable to do.

The procedure of transfusion-in-utero is almost past the experimental stage and soon will become a standard method of treatment in severe cases of haemolytic disease.

Other methods have been tried experimentally in order to increase the salvage rate of this disease.[1]

(1) Operative exposure of the foetus in- with direct exchange transfusion using the femoral vein. So far, all of these attempts have been followed by premature labour before the age of viability.

(2) Erythropoietic grafting of the foetus with Rh-negative hematopoietic tissue prepared from the liver of dead donor foetuses. The attempt is made to replace the foetal marrow with erythropoietic tissue producing Rh-negative red cells. The graft would only last a short while, eventually being destroyed by homograft reaction. However, before being rejected by the host, the graft would function to produce Rh-negative red cells. Hopefully, this function would continue long enough and well enough to bring the foetus to term. This method is like a prolonged intra-uterine transfusion, but eliminates the need for repeated entry into the amniotic sac. So far such attempts have not been successful.

(3) Prophylaxis, by injecting Rh-negative primiparous women at delivery with large doses of donor anti-Rh antibody. This is based on the assumption that most of the sensitization for subsequent pregnancies comes from the trauma and blood loss of delivery. By doing this, the Rh-positive foetal cells would be destroyed before they could act as antigens. It is now known that sensitization occurs steadily during pregnancy and not just during delivery, thus invalidating this attempt at controlling the severe cases of Rh disease.

(4) Supression of antibody production in previously sensitized women. Cortisone and A.C.T.H. have been given in an attempt to inhibit the production of anti-Rh antibodies. They have failed. The use of stronger drugs such as 6-mercaptopurine has been suggested but never attempted.

(5) Mechanical removal of maternal anti-Rh antibody by plasmophoresis. Instead of lowering the antibody titre as expected, this procedure results in a stimulation of antibody production and a rise in titre.

CONCLUSION

The concept of Rh-hemolytic disease of the newborn has been discussed, with emphasis on the means of diagnosis and management. The results are encouraging but not yet perfect—babies still die from this disease. However great strides have been made in improving what was considered, until recently, an untreatable condition. These improvements serve as stimuli in the continuing search for better means of managing this disease.

ACKNOWLEDGEMENT

Appreciation is extended to Mr. R. B. Roy, Technical Director, Blood Bank & Rh Laboratory, Toronto Western Hospital, for his advice and criticisms as well as for the graphs and photograph used in this article. The interest of Dr. H. Bain of Hospital for Sick Children is also gratefully acknowledged as is the encouragement and work contributed by Mrs. G. J. Douglas.

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The Management Of Athletic Injuries

J. D. Richardson 6T6

INTRODUCTION

In the last twenty years there has been a great increase in the number of athletes competing in organized sport. Not only has there been an increase in the number of professional athletes, but a great rise has been seen in the number of teenagers taking part in athletic programmes in high school, college, or in the local communities. Naturally, when these players are involved in body contact sports, even with the use of advanced safety equipment, there has been an increase in the number of injuries which must be managed. It is essential that experienced medical personnel be available to advise in the prevention of injury, to prevent fatalities, to diagnose and manage injuries, and to return the players to the game.

The branch of Medicine which deals with this type of injury has also seen many advancements and changes in the last twenty years. Today, the team physician, the family doctor, the intern in the hospital emergency deparment, and the surgeon must all be aware of the types of injury which occur in contact sports in order to make an accurate diagnosis and outline a programme of management. In this article, I shall comment upon only a few of the more common and important injuries which confront the physician or surgeon, and briefly point out a few important points in their diagnosis and management.

A. Soft Tissue Injuries

The most common type of injury seen in contact sports is the soft tissue injury. These include the sprains of ligaments, the strains of muscles and tendons, and the contusions or bruising of joints and muscles. Together, these form about 65% of all injuries seen in contact sports. Although they may not be serious enough to require a doctor's attention, the team trainers previously instructed in a programme of management by the team physician will avoid unnecessary discomfort and disability of the players.

A very common example of this type of injury is the simple contusion of the anterior aspect of the thigh—the "Charley Horse". Loose, poorly positioned thigh pads are often indirectly responsible. Usually the injury consists of bruising of all soft tissues between the skin and the bone. Bleeding occurs within the muscles; muscle fibers are broken; and subcutaneous fat is liberated from its confines. All these lead to inflammation, edema, ecchymosis, pain and immobility, and interference with function of the area involved.

Often it is difficult to determine the severity or extent of such an injury in the first 24 hours. However, management of such an injury should begin when the player comes to the bench. The injured limb should be put to rest—the player withdrawn from the game; the leg elevated; and cold in the form of an icepack applied to the injured area. Also a tensor bandage may be applied firmly around the thigh. Sometimes it is helpful to cover the injured area with a square of half or one inch thick foam rubber padding held firmly in place with a tensor bandage.

Rest, elevation, cold and compression are all that is usually required for the first twenty-four hours, other than relief of pain and discomfort with ASA and codeine.

There is considerable controversy as to the benefits of using oral proteolytic enzymes such as Carica papaya (Papase) for this type of injury. Some team physicians feel that proteolytic enzymes act to reduce inflammation through their ability to depolymerize fibrin and other protein substrates. By virtue of this, edematous fluid and depolymerized, proteinaceous tissue debris are more easily reabsorbed, pain is reduced and mobility is restored. For the large "Charley Horse" and other contusions, some team doctors add a preparation such as this to their armamentarium in an attempt to achieve this purpose. For example Papase tabs. 2, q,2,h. for two days followed by tabs. 2, t.i.d. for four days, sublingually is suggested.

The soft tissue injury of the thigh is reassessed again after twenty-four hours. From this point, rest, compression and support, and a comfortable amount of heat are used. Activity with or without weight bearing is dependent upon the amount of pain produced. When acute pain and tenderness have subsided, progress exercises are begun, leading to gradual return of full function. Heat in the form of a comfortable heating pad or short-wave diathermy t.i.d. for 15 minute periods can be used. Massage is also valuable. However once pain and discomfort are lessened, only time is required to rebuild tissue.

When the Charley Horse of the thight extends down to the bone and crushes the muscle fibres attached to the femur, formation of bone may occur in the associated blood clot as nature attempts to heal the junction of muscle and bone. This over-production of bone may be palpable in the muscle and may also be seen radiologically. This bone if left alone will reabsorb, often quite slowly; but surgical removal is unnecessary.

These principles as outlined in the above example can be applied to any soft tissue contusion or strain involving muscles, ligaments, and joints.

B. The Head Injury

General

Death resulting from an athletic injury is relatively uncommon—a survey of deaths occuring in American high school football players showed an incidence of 1 death for every 10,000,000 man-hours-exposure. The head injury is the most frequent killer, followed by the fractured cervical vertebra, the ruptured spleen, and heat prostation. A blow to the head may lead to either a subdural or extradural haemorrhage with varying dangers.

Group 1

This group includes the more common and less severe "concussion". These are the players who have sustained direct or indirect trauma to the head sufficiently severe to render them momentarily unconscious or disoriented. In order to remain in this group, the injured athlete should completely recover neurological function, both mentally and physically immediately following this momentary alteration of consciousness. Even in this group, a small number may develop a subsequent intracranial hematoma.

Management:

Remove the player from the game. Ideally after a concussion such as this, the patient should be observed by trained medical personnel for at least twenty-four hours. Often circumstances and facilities do not allow this type of management. When hospitalization is refused or not available, frequent observations of the patient during the next twenty-four hours by a capable person is suggested.

The patient should be awakened every hour and the observer should note— (1) the ease with which the patient may be aroused, (2) the state of consciousness, (3) the equality of the pupils, (4) the normality of the pulse, and (5) that there is no malfunction of one or more of the extremities. Also headache, visual disturbances, nausea, or any other abnormal behaviour should indicate the need for re-evaluation. Even after twenty-four hours, the above signs and symptoms are significant and demand further investigation.

Not uncommonly, a great deal of pressure is exerted on the physician either by the patient himself, the coach or well meaning friends to allow the athlete to return to the team immediately. The physician alone should make the decision. It is recommended even if no significant signs or symptoms have occured after twenty-four hours, that these athletes should not engage in contact sports for at least one week.

Group 2

These are the players whose loss of consciousness is more than just momentary and who are slow to clear mentally. This, at the very least, means some form of contrusion of the brain. Nausea, vomiting, persistent headache, unsteadiness, or any transient neurological deficit are definite evidence of more severe injury to the brain.

Management:

Remove the player for the rest of the game. Take the patient to the Emergency Department of the local hospital. Observe the level of consciousness, record the pulse and respiratory rates, and take the blood pressure every fifteen minutes until stable and then hourly for twenty-four hours.

Any deviation from normal, or deterioration in the level of consciousness, i.e. increasing drowsiness, or disorientation should prompt an emergency neurological consultation. The classical dilatation of one pupil, increasing motor or sensory deficit, or nerve malfunction are later and more ominous signs. A series of skull x-rays may be useful in order to demonstrate a suspected fracture or a shift of the Pineal gland. Also periodic Echo encephalograms may demonstrate a deviation of the intracranial midline structure suggesting unilateral intracranial haemorrhage.

Even if the player does not show any of these more severe or progressive signs and symptoms during the first twenty-four hours, he should still refrain from participation in any type of sport for at least two weeks.

Group 3

These are the athletes (a) who remain unconscious, or (b) who have depressed or compound fractures of the skull with or without neurological deficits or (c) those who have progressive neurological signs and symptoms as listed under the above two groups.

Management:

Admit the player to the local hospital. As in group two observe the level of consciousness, record the pulse and respiratory rates, and take the blood pressure every fifteen minutes until stable, and then hourly for twenty-four hours or in some cases longer. Ensure a patent airway; loosen the patient's collar or athletic equipment; place the patient on his side with the corner of his mouth dependent. DO NOT administer narcotics or sedatives. These can depress respirations, lead to an increased intracranial pressure, alter the state of consciousness and alter the pupillary signs.

The patient should have an emergency consultation by a neurologist or neurosurgeon. No attempt to outline the neurosurgical management of such a patient, will be made here other than to mention that such procedures as emergency burr holes strategically placed may be life saving and can be done by any qualified physician in the absence of a neurosurgeon.

Following such an injury, no matter how complete the recovery may seem, the player's further participation in contact sports should be prohibited.

C. Chest & Abdominal Injuries

(a) *Fractured Rib and Costochondral Separation*

These injuries do occur occasionally, usually from a fall or a blow to the anterior or lateral chest wall. Severe pleuritic pain begins immediately after the injury and may last for twelve to twenty-four hours. Most commonly the fractures are linear without displacement and without injury to the pleura or underlying lung.

Management:

(1) The pain can be relieved by injection of lidocaine HCL 2% in adrenalin as an intercostal nerve block at a site along the nerves proximal to the fracture. Some authors suggest the addition of hydrocortisone along with the lidocaine. (2) A chest x-ray should also be taken to confirm the diagnosis and to rule out pleural or pulmonary complications. (3) Adhesive strapping is used by many, to splint the chest wall. The use of an adjustable canvas belt is an alternative to the strapping.

(b) *Contusions of the Chest Wall*

These can be managed by applying the principles outlined under the section on soft tissue injuries. Remember, a blow to the lower left chest wall may be associated with an underlying splenic rupture.

(c) *Muscle Tear of the Abdominal Wall*

These injuries are associated with tenderness and spasm of the muscle wall of the abdomen. The management is the same as that for a soft tissue injury. Its importance is the possibility of underlying internal injury.

(d) *Ruptured Spleen*

Next to death as a result of intracranial haemorrhage and cervical injuries, this is the most common cause of fatality. Usually this injury results from a direct blow to the splenic area. Occasionally an indirect blow initiates it. Remember that the player suffering from Infectious Mononucleosis has an increased suscepibility to this type of injury and therefore should be barred from contact sports during the acute phase of his illness. The diagnosis of ruptured spleen is made from the history of an injury together with the clinical findings. Following a blow to the splenic area, evidence of impending shock — sweating, paleness, rapid and thready pulse, and collapse are evidence for hospitalization. Pain and tenderness may be localized to the upper left portion of the abdomen or diffused. Left shoulder tip pain, rigidity in the left flank, a mass in the splenic area, and a bloody paracentesis are all suggestive signs. Delayed rupture of the spleen may be another mode of presentation. With the formation of subcapsular hematoma, these signs and symptoms may not be present for hours, days, or even months following injury.

Management

Laparotomy, splenectomy and thorough exploration to rule out associated injury is indicated. Usually the player is out of contact sports for at least one month.

(e) *Ruptured Kidney*

Usually resulting from a blow to the loin. Death from massive haemorrhage may ensue, or a degree of haemorrhagic shock may be associated with gross hematuria. Any player receiving a blow to the region of the kidney should be instructed to void, and the urine examined for pink tinged or frank blood. If hematuria is noted, the player should be removed from the sport and fully investigated for renal damage including an IVP before returning to active participation. The management of a ruptured kidney, can be found in routine surgical textbooks.

(f) *Ruptures of the Liver and the Bowel*

These injuries are less common, and I will only list them as possible injuries following a blow to the abdomen.

D. Injuries of the Lower Extremity

(a) *Injuries of the Knee*

The knee is a very common site of injury in the athlete. In the classical knee injury, the trauma results from a blow to the side, or lateral blocking or checking. Usually the foot is fixed on the ground with the knee partially flexed. With the blow the knee is forced inward causing the thigh to rotate inward and the leg outward. Stress is primarily received on the ligaments on the inner side of the knee. As the foot is forced into external rotation, stress comes against the medial collateral ligament of the knee, the superficial layer taking the strain first. As this stretches, tears, or gives way, the force is transferred to and damages the deep layer to which is attached the medial meniscus. If the force continues, the anterior cruciate receives the stress and it too, may be traumatized. In severe injuries the medial meniscus may also be torn between the femur and the tibia. Together these three injuries form the "Terrible Triad".

(1) *Management of Mild Injuries to the Ligaments*

The signs and symptoms of a mild strain, for example, to the Medial Collateral Ligament include (a) tenderness at the site of the tear, (b) pain on active use of the knee, (c) local swelling at the site of the injury, (d) pain on forced motion or on attempt to duplicate the motion which caused the tear. Important negative findings are (a) no instability, (b) no blood in the joint or infiltrated through the tissues, (c) no effusion, (d) no locking, (e) no pain or normal passive movement.

The treatment of these very common injuries is basically that of a soft tissue injury as discussed earlier. It includes immediate application of a pressure bandage, ice packs, rest and elevation for twenty-four hours. After this time, if the player is not experiencing acute

distress on movement, he may gradually return to full participation. Heat and quadiceps exercises will speed up complete recovery. The knee may be strapped for added support and comfort when the player resumes play.

(2) *Moderate Injuries to the Ligaments*

In this type of injury, it is assumed a ligament of the knee has been partially torn. The findings are similar but more pronounced than those of the mild injury. Again positive findings include (a) pain in the knee, (b) tenderness at the site of injury, (c) disability of a greater degree than in the mild type, (d) swelling at first localized to the area of damage, later spreading to become a diffused swelling about the joint, (e) blood or fluid in the joint, (f) pain on reproduction of the force and direction of the injury and (g) locking if the meniscus has also been affected. Negative findings include no execessive lateral motion or increased antero-posterior slipping of the tibia on the femur with the knee flexed, i.e., no positive drawer sign.

Management:

Again a firm compression bandage, ice packs, elevation, and rest are used for the first twenty-four hours. The joint should be x-rayed to rule out possible bone damage. Aspiration of local hematoma or joint effusion under aseptic procedure may be required periodically.

Pain can be relieved with ASA and Codeine. Plaster splints are not necessary; elastic wraps are sufficient to protect the ligaments from further damage. After twenty-four to forty-eight hours, the injury is reassessed. If acute discomfort is still present, weight bearing is avoided, and gentle quadriceps exercises are begun. With decreasing acute discomfort, increased activity is allowed. Controlled physical therapy such as short-wave diathermy, electric heating pads, and whirl pool treatments are useful. With improvement, immobilization is replaced by protective strappings. Usually the player may return to the game when he can participate without acute distress—the common period being one to three weeks after injury.

(3) *Severe Injuries to the Ligaments*

This is the injury in which there has been complete loss of function of one or more of the major ligaments of the knee. Most commonly, this is the medial collateral ligament, particularily at its superficial tibial attachment. The positive findings include (a) a history of a knee that has "given way", (b) extreme diffuse pain, (c) local pain at the site of injury, (d) abnormal movement of the joint—lateral instability with the knee slightly flexed, or a positive drawer sign. These very important latter signs can only be demonstrated very early after the injury before they are masked by swelling and muscle spasm; or they can be seen if the player is given a general anaesthetic and the joint manipulated.

Management:

Again for the first twenty-four hours compression, ice packs, rest, and elevation along with the relief of pain with ASA and Codeine are used. An x-ray is also taken. With demonstrative collateral or anterior cruciate instability, a surgical repair of the torn ligaments within ten days of the injury is suggested. Post-operatively, a posterior plaster splint is applied, and rehabilitation with progressive quadriceps and hamstring exercises is begun. Periodic effusion may require aspiration. The player is usually out for that season, but commonly will return to full active competition the next one.

(4) *Injuries to the Meniscus*

The tear of the medial meniscus of the knee is often associated with tears to the medial collateral and/or anterior cruciate ligaments. Often it may be associated with repeated strains to the knee. The positive signs include (a) a clear and definite history of clicking of the knee following a twisting injury, and (b) a positive arthrogram with the radio-opaque dye outlining the tear in the meniscus. Remember that a negative arthrogram may be seen even with a significant tear of the cartilage. Other suggestive findings include tenderness along the joint line in the area which is damaged, unilateral clicking in the knee on passive movement, a knee which gives way, and a knee which resists conservative treatment.

The management of this injury is the surgical excision of the torn meniscus.

(b) *Injuries of the Ankle*

The ankle is another very common site of ligamentous injuries. Some sports seem ideally designed to hurt the ankle. Football, soccer, and basketball involve quicks turns on a fixed foot, and skiing adds the enormous power of an eight foot lever strapped to the sole. Some of these injuries can be avoided by wearing ankle wraps and properly laced boots.

The ligaments which are most commonly involved are (a) the fibular collateral, (b) the deltoid, and (c) the tibio-fibular ligaments. A twisting force of the ankle may result in the partial or complete tearing of one or more of these ligaments, with or without an associated fracture of the fibula or tibia. In this article, the management of the more common strains, sprains, and tears of these ligaments without associated fractures will be discussed.

During the initial examination, the history of the injury, the point of maximum tenderness, the degree of local or generalized swelling, the degree of joint instability, and the degree of disability should be noted. X-ray examination of the joint is also necessary to rule out any associated fracture.

If no evidence of fracture is seen on radiological examination again the principles of soft tissue injury are applied. Cold, compression, rest, elevation, and anal-

gesia with ASA and Codeine are the means of treatment for the first twenty-four hours. Often an effusion within the ankle joint follows such an acute injury. If the joint is properly entered, small amounts of blood (10 cc.) can be aspirated, and 15 mg. hydrocortisone acetate can then be injected directly into the joint to give profound relief of pain. Compression for the first twenty-four hours is achieved by the use of a tensor bandage. This allows sufficient compression to prevent extensive edema without being uncomfortable. Every team physician has his own method of applying a compression bandage. One of the most effective is the modification of the Louisiana ankle wrap. This employs a three inch tensor bandage as follows. See figure 1.

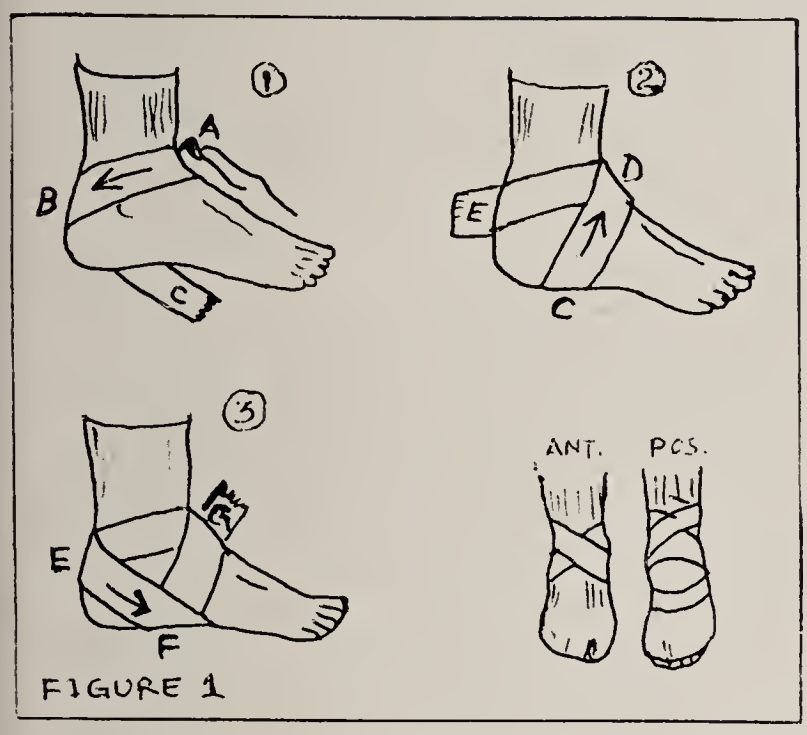

FIGURE 1

1. The start (A) of the tensor, crossing the top of the ankle above the lateral malleolus (B) around under the heel from the inner side (C) 2. The tensor crosses the dorsum of the foot (D) around the inner side of the ankle above the medial malleolus (E) 3. The tensor crosses the outside of the heel under the plantar surface of the foot (F) to terminate at (G) the starting point. The tensor then continues until the bandage is exhausted with suitable overlapping of the turns so that one turn is not directly superimposed over the one beneath. This application should be made snugly but not tight enough to interfere with circulation. A little practice will determine the degree of tension necessary.

After twenty-four to forty-eight hours the ankle is then reassessed. At this time the degree of edema, ecchymosis, and disability is observed. Heat therapy and gentle centripedal massage can be started along with whirl-pool bath treatments. After this a more stable strapping can be applied. The hair is shaved from the lower third of the leg, coated with Friar's Balsam, and a three inch elasticized tape is applied to the ankle, while it is held in its normal anatomical position, in the same manner as the tensor bandage was initially applied. The collateral ligaments may also be reinforced with vertical strips of two inch tape. Weight bearing is permitted as soon as natural walking is possible.

The ankle is reassessed ever two to three days; the strapping is removed, heat therapy and massage are given, and the strapping is re-applied. When the pain and tenderness approach the vanishing point, the strapping is removed. This may be from one to three weeks. When the player returns to the game, he should tape his ankles for prevention of further injury.

More than occasionally on initial examination, an instability of the ankle mortice is noted, with subluxation of the ankle joint. Often this can be clearly demonstrated radiologically with special stress films. If the severity is such that the examiner or player feels abnormal mobility at the ankle joint, or if the degree of pain and swelling is more profound than usual, then the patient should be given a general anaesthetic, and stress films taken.

If a subluxation of the joint is shown, suggesting that there has been a complete tear of one of the ankle ligaments, early surgical repair is the preferred method of management.

E. Injuries of the Upper Extremity

In this article, the management of all of the injuries of the upper extremity seen in sports will not be discussed. A list of the common ones and the management of the one most often missed follows. Most often an injury of the upper limb results from a fall on the outstretched hand. A list of the possible injuries sustained in this manner would include; strains and partial dislocations of the fingers and thumbs; fractures of the scaphoid; Colle's and Smith's fracture; strained wrist; fracture of the shaft of the radius and or ulna; fracture of the head of the radius; fracture of the olecranon; dislocation of the elbow; supracondylar fracture of the humerus; fracture of the shaft of the humerus; shoulder dislocation; rotator cuff tear; shoulder separation; fracture of the clavicle; and stern-clavicular dislocation. These are all covered well in standard texts of general surgery and orthopaedics.

However, one fracture, the diagnosis of which may be easily overlooked — viz, the fracture of the scaphoid bone should be emphasized. Often this may be missed unless the team physician is looking specifically for it, following the so called "sprained wrist". The most significant sign is localized tenderness in the anatomical snuff-box. Extensive initial radiological examination may fail to demonstrate a fracture in many of these cases. However, if the X-ray is repeated in 10-21 days, a widened fracture line is usually seen.

With localized tenderness, even without a radiologically demonstrable fracture initially, a cast should be applied to the forearm with the wrist and thumb in the position of grasp. The thumb is best immobilized up to the interphalangeal joint. If no fracture is seen on the

initial X-ray, the cast may be removed after 3 weeks and re-X-rayed. A demonstrable fracture line requires the re-application of a cast. This cast may be removed in 6 weeks and progress of union determined by another series of X-rays. Occasionally tomographs may be useful in assessing union. Typically this is a slow fracture to heal and immobilization for 16 weeks is often seen.

The application of a scaphoid cast is not a contra-indication to resuming contact sports. It has been known for a Canadian professional quarterback to play with a reinforced cast on his non-passing arm.

In conclusion, remember that an athletic injury is no different than any other, except that a higher incidence of injury is found in sports than in everyday living. Remember that we are dealing with people not anatomical areas, and that kindness and compassion are therapeutic adjuncts which always aid in our purpose.

ACKNOWLEDGEMENT

I would like to thank Dr. J. W. Charters, Physician for the Hamilton Tiger-Cat Football Club for his assistance in the writing of this article.

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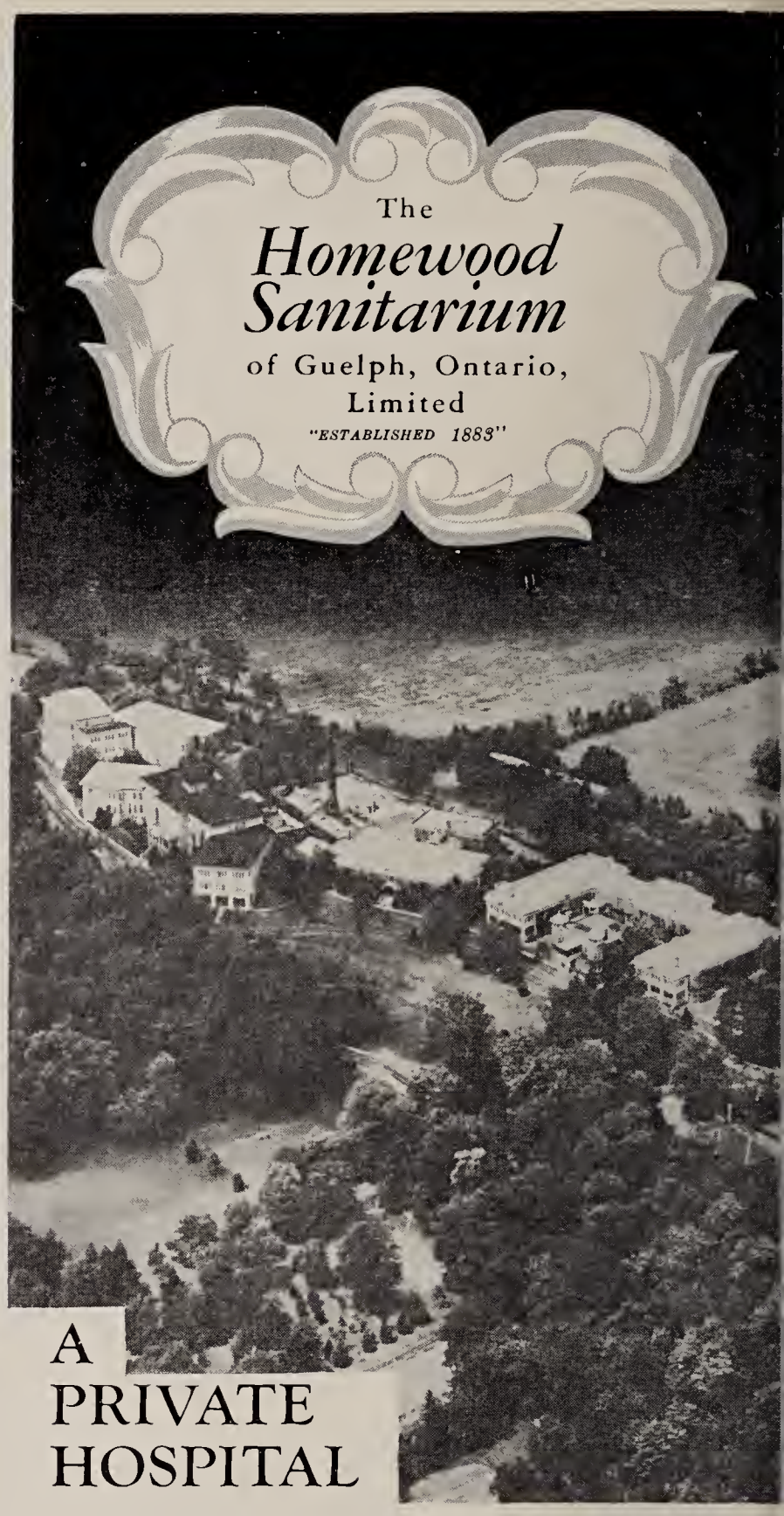

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Heinrich Romberg

"If the patient is ordered to close his eyes while in the erect posture, he at once commences to totter and swing from side to side."

The year was 1840, the disease was tabes dorsalis, and the above sign became known by the name of the man who described it—Romberg's sign.

Moritz Heinrich Romberg was born in Meiningen, capital of the former Duchy of Saxe-Meiningen and since 1946 just inside the border of East Germany. He was educated in Germany and in 1817 graduated from medical school at the University of Berlin. Romberg's inaugural dissertation, presented for graduation, was on the subject of congenital rickets, one which he never again wrote about as his interest became focused on the new field of neurology. After his formal education was completed, he remained in Berlin, and in the course of time became professor of medicine and director of the Royal Polyclinic Institute of Friedrich Wilhelm University.

Romberg was the author of the first classification of diseases of the nervous system. He was critical of the failure of his predecessors to prepare a work on nervous disorders worthy of this segment of clinical science. His "Lehrbuch der Nervenkrankeiten" which was written in 1840 emphasized the significance of physiological principles in interpreting neurological function. In the preface to his first edition, Romberg wrote thus concerning the lack of progress in the study of neurological diseases.

"The blame lies in a measure with the distinguished members of our profession who have been deterred by a fear that pathological investigations would fail to cope with the advanced state of physiological inquiry; in others, the fault is to be attributed to that mental indolence, which gives the preferenece to the easy path of tradition, and with foolish scepticism rejects everything that is new. But in no department of pathology has physiology exerted so great an influence, no where has free research achieved so glorious a victory over dull, traditional routine, as in the doctrine of Nervous Diseases. This present work, the fruit of twenty years of research, is intended to afford evidence of this fact. I feel assured of the existence of numerous defects and errors as I know that it will only serve as a state of transition to more perfect works; but the foundation upon which it has been constructed is not to be shaken, as it is "the physiological principle"; this is based upon the unchangeable functions of the animal economy."

The classification of Romberg followed Cullen's doctrine of neurosis: dysfunction of sensibility and dysfunction of motion. Each dysfunction was subdivided, following the delineations of Whytt, published a century earlier. Hyperesthesia and anesthesia, the subdivisions of the neuroses of sensibility, are concepts that remain in current use, whereas hyperkineses (spasms) and akineses (paralyses) were neuroses of motion. Ciliary neuralgia was presented as a neurosis of sensibility, whereas ataxia in syphilis of the central nervous system was presented as a neurosis of motility. The chapter on the latter neurosis contains the following paragraphs.

"The spinal cord viewed as a central organ, not only serves as an agent for the mutual transmission of stimuli, but also as a source of nervous power, of the principle of motor and sensory tension, by which the continuance and vigour of motion and sensation is secured, and a general stimulus for the entire organism provided. The disease which is characterized by a diminuation of this power is termed tabes dorsalis.

Early in the disease we find the sense of touch and muscular sense diminished, while the sensibility of the skin is unaltered in reference to the temperature and painful impressions. The gait begins to be insecure and the patient attempts to improve it by making a greater effort of the will; as he does not feel the tread to be firm he puts down his heels with greater force. From the commencement of the disease the individual keeps his eyes on his feet to prevent his movements from becoming still more unsteady. The insecurity of his gait exhibits itself more in the dark.

Painful sensations of different kinds almost invariably accompany the affection; the most common is a sense of constriction, which proceeds from the dorsal or lumbar vertebrae, encircles the trunk like a hoop, and not infrequently renders breathing most laborious. Several of my patients have described this sensation as particularily troublesome during sleep, causing them suddenly to start up and scream out. . . . The necessity of employing his eyes becomes more and more urgent; if he closes his eyes, even while sitting, his body begins to sway to and fro; . . . Even where the optic nerve was not implicated, I have repeatedly found a change in the pupils of one or both eyes, consisting in a contraction with loss of motion, which in one case, that of a man aged 45, attained to such a height that the pupils were reduced to the size of a pin's head!

Although the post mortem records of this disease may present considerable variations, they almost without exception show the existence of partial atrophy of the spinal cord; the lumbar portion and the nerves given off from it are the parts generally affected."

Romberg carefully described other diseases in his book but the emphasis was firmly placed upon the

(Continued on page 128)

On Inspection - Answers

1. a) Kerley's "B" Line
   Causes—
   1. Dilated lymph channels especially in mitral stenosis. Also seen in lymphangitis carcinomatosis where the lymphatics are dilated due to obstruction by large numbers of carcinoma cells in the lumen.
   2. Thickened interlobular septa due to engorgement of the lymphatics and veins which run in the septa producing oedema of the septa. This is not infrequent in mitral stenosis. Hemosiderin deposits in and around the septa make it even more conspicuous. Thickening of the septa may also occur in some cases of emphysema and pneumoconiosis.
   3. Engorgement of the peripheral vessels. Also seen in some cases of mitral stenosis. In very thin, normal persons, even the normal vessels may be visible as line shadows.

   b) Diagnosis—Mitral stenosis with prominent Kerley's "B" Lines. Note also the increased vascular markings in the lungs caused by venous congestion and the straight left heart border produced by enlargement of the left atrium and right ventricle and the left ventricle remaining normal in size.

2. a) This appearance is called consolidation and is due to replacement of alveolar air by fluid or cells.

   b) Diagnosis — Right upper lobe pneumococcal pneumonia.

   c) The onset is very abrupt with shaking chills, rapid rise in temperature and corresponding tachycardia.

   d) 1. Patient appears acutely ill.
   2. Pleuritic pain and cough producing rusty sputum.
   3. Respiration rapid, shallow and grunting with dilatation of the alae nasi and mild cyanosis.
   4. Diminished or absent rib movements on affected side.
   5. Increased tactile femitus over affected area.
   6. Percussion note dull over affected lobes.
   7. High pitched bronchial breath sounds.
   8. Whispering pectriloquy.
   9. Fine, moist rales.
   10. Temperature 102.5 to 105° F.

   e) Course — Within 12 to 36 hours after initiation of penicillin therapy, temperature, pulse and respiration return to normal, pleuritic pain subsides and the spread of the inflammatory process is halted.
   Complications —
   1. Atelectasis
   2. Carnification
   3. Lung abscess
   4. Pleural effusion
   5. Empyema
   6. Pericarditis
   7. Arthritis
   8. Acute bacterial endocarditis
   9. Meningitis

3. a) Diagnosis—Left ventricular aneurysm.

   b) Occurs after myocardial infarction within weeks or months of the acute attack.

   c) Characteristics of the pain—
   1. Onset not necessarily related to exertion.
   2. Quality—constricting.
   3. Location—substernal.
   4. Radiation—down inside of the left arm or both arms and up into the neck or even the jaw and through to the back.
   5. Severity — very severe. Patient feels weak and may faint.
   6. Progression—reaches a peak rapidly and remains there.
   7. Duration—longer than 30 minutes.
   8. Aggravation — not affected by movement, breathing or swallowing.
   9. Relief—by hypo. Not by rest or nitroglycerine.
   10. Associated symptoms—skin cool, pallid and profusely sweating. Dyspnoea, weakness and faintness occur. Nausea and vomiting are common.

   d) Prognosis—Aneurysm practically never ruptures and prognosis usually does not differ from that of a healed myocardial infarction.

4. a) Coin Lesion

   b) A. Infective
   1) Acute bacterial pneumonia
   2) Lung abcess
   3) Granulomatous
   (a) Bacterial
   (i) TB focus
   (ii) Syphilitic gumma
   (b) Mycotic
   (i) Cryptococcus neoformans (Toruloma)
   (ii) Aspergillus fumigatus (Mycetoma)
   (c) Non-specific granuloma

   B. Neoplasms
   1) Malignant
   (a) Bronchogenic carcinoma
   (b) Sarcoma
   (c) Secondary metastases to lung e.g. renal cell carcinoma and carcinoma of the colon
   2) Bronchial Adenoma (75% are benign)
   3) Benign
   (a) Fibroma
   (b) Hamartoma (really a developmental abnormality, not a Neoplasm)

   C. Fluid-containing cysts
   1) Hydatid
   2) Developmental

   D. Arteriovenous aneurysm

   E. Pulmonary infarct

   c) Diagnosis is anaplastic carcinoma of the lung.

Recent Advances

The Neurosurgery Of Hydrocephalus

DEFINITION

Hydrocephalus is a distension of the cranium due to an increase in the volume and pressure of cerebrospinal fluid.

HISTORY

"The most successful surgical procedure for arresting hydrocephalus is the removal or fulguration of the choroid plexus of the lateral ventricle".[1] Repeated needle drainage of the ventricles was a palliative procedure often attempted, but the hazards of infection and trauma, coupled with the poor results of such techniques made this a most unsatisfactory procedure.

Fortunately, fulguration and needle drainage have been succeeded by many safer and more effective procedures.

ETIOLOGY

Cerebrospinal fluid is normally in continuous communication with the sub-arachnoid villi along the sagittal venous sinus. The fluid escapes from the ventricular system via the foramina of Magendie and Luschka. It then passes through the cisterna magna and the various sub-arachnoid spaces beneath the brain stem and thalamus, and travels around the cerebral hemispheres to reach the superior convexity of the brain. It is suggested that spinal cerebrospinal fluid drains locally through vertebral venous plexuses, the intervertebral veins, and the posterior intercostal and upper lumbar veins, into the azygos and hemiazygos veins.[2]

In communicating hydrocephalus, cerebrospinal fluid has free access to the sub-arachnoid spaces. In the obstructive type, the cerebrospinal fluid cannot escape the ventricular system. Occasionally, the over-production of fluid by a choroid plexus adenoma will produce hydrocephalus in the presence of a patent drainage and reabsorption system. However obstruction to flow is the important cause, and the etiology in the pediatric age group will be discussed under the following divisions:

1. Neoplasm
2. Congenital Malformation
3. Inflammatory and Post-inflammatory Reaction

1. Neoplasm

The treatment of hydrocephalus due to obstructive and inoperable tumours is to shunt cerebrospinal fluid around the point of obstruction. In infancy, gliomas of the cerebellum, pons or medulla, obstruct the fourth ventricle or the caudal opening of the aqueduct of Sylvius. Rarely, dermoids or choroid plexus adenomas will also do this. Brain stem and basal ganglia gliomas, and pineal tumours obstruct the posterior third ventricle and aqueduct. The anterior third ventricle may be compressed by a cranio-pharyngioma, or a colloid cyst of a lateral choroid plexus may obstruct the foramen of Monro.

2. Congenital Malformations

(a) Spina Bifida and Cranium Bifidum:

44% of children with myeloceles, and 23% with meningoceles develop hydrocephalus within a few weeks.[3] The frequent association of hydrocephalus with other concomita of spina bifida is well-known. Hydrocephalus is nearly always present with the Arnold-Chiari malformation, due to the obliteration of the sub-arachnoid pathways around the brain stem and upper cervical cord.[4] Encephalomyeloceles in the suboccipital region, with their obliteration of the cisterna magna due to various posterior fossa malformations, cause an associated hydrocephalus.

(b) Stenosis of the Aqueduct:

Russell describes a subdivision or forking of the aqueductal channel into many minute tubules.[5] Actual congenital stenosis or web is rare.

(c) Gliosis of the Aqueduct:

This is a progressive overgrowth of sub-ependymal neurolgliz which occludes the aqueduct.

(d) Vascular Malformation:

Congenital A-V aneurysm of the posterior cerebral artery, and the vein of Galen or the straight sinus, may occlude the aqueduct.

(e) As a point of interest, Edwards has reported on four families where "The pattern of inheritance of hydrocephalus is entirely consistent with recessive sex linkage".[6] He suggests that the cause is a variety of aqueductal stenosis related to a mutation on the X-chromosome.

3. Inflammation and Post-Inflammatory Reaction

Intracranial bleeding at or before birth may result in fibrosis of the leptomeninges at the base of the brain, and obliteration of the sub-arachnoid spaces. Communicating hydrocephalus may be the only clinical sign of the incident.

Post-meningitic obliteration of the sub-arachnoid pathways is a recognized sequela of meningitis even after antibiotic "cures". Atypical, mild cases of meningitis may present later with an "iodiopathic" hydrocephalus.

TREATMENT

If the hydrocephalus is present as a result of a tumour, the treatment of choice is the removal of the tumour. However, when this is not possible, the development of cranial distension and damaging cerebral compression can be avoided by shunting fluid around the obstruction, or out of the ventriculo-sub-arachnoid system entirely. The shunts need not be regarded as strictly palliative measures to be performed on children doomed to die of underlying malignancy or progressive adhesions. Indeed, many cases of communicating hydrocephalus become spontaneously arrested after decompression allows space for the sub-arachnoid channels to open up. Estimates of such arrests range up to 45%.

Choroid plexectomy has been abandoned except for frankly malginant tumours of the plexus-cells. The following quote illustrates the uselessness of this procedure: "Favorable results from this procedure have been in patients in whom spontaneous arrest was imminent, or in whom the circulation and absorption of cerebrospinal fluid were impaired to a minor degree only".[7]

Four fascinating but now largely abandoned shunt procedures are briefly described.

Arachnoid-Ureterostomy

This procedure is designed for the relief of communicating hydrocephalus. Cerebrospinal fluid is channelled from the region of the cauda equina, through divided para-spinal muscles, into the left ureter, after a left nephrectomy. Infection, revisions of the length of the communicating tube due to growth of the child, and blockage, are frequent sequelae. The continuous drainage of electrolytes, especially of sodium, renders the patient susceptible to electrolyte imbalance in the event of even mild stress disturbances of the fluid balance. Also, the loss of a kidney may prove to be disastrous in later life.

Ventriculo-Ureterostomy

Here, cerebrospinal fluid is shunted from behind the obstructive lesion into a ureter, after nephrectomy. Infection, blockage, electrolyte loss, frequent growth revisions, and the loss of a good kidney are disadvantages.

Ventriculo-Peritoneostomy

To avoid nephrectomy in a child with one diseased kidney, cerebrospinal fluid is shunted parallel to the spinal cord, then into the peritoneal cavity. Aside from the aforementioned sequelae, the peritoneal end of the tube is especially susceptible to blockage, and is difficult to re-open.

Third Ventriculostomy

W. E. Dandy described a method for the relief of hydrocephalus due to obstruction at or near the rostral end of the aqueduct.[8] The anterior projection of the floor of the third ventricle is opened into the cisterna chiasmatis. This charmingly simple solution is usually unsuccessful if performed within a few months of birth, since the cisternae and surface pathways, never having carried fluid, are poorly developed. The opening either seals over, or a sub-dural accumulation of cerebrospinal fluid results.

Ventriculo-cisternostomy (the Torkildsen procedure) and ventriculo-auriculostomy are the most widely-used and promising methods for the relief of hydrocephalus. These will now be described in some detail.

The Torkildsen Ventriculo-cisternostomy[9]

INDICATIONS

(i) Inaccessible obstruction in the third ventricle or in the aqueduct of Sylvius.

(ii) Obstruction of one or both (in which case a bilateral shunt is performed) foramina of Monro.

(iii) Obstruction of the outflow forámina of the fourth ventricle.

DESCRIPTION

A paramedian occipital burr hole is made, and the dura opened. Next a ventricular needle is introduced through the hole into the occipital horn of the lateral ventricle, and 5 to 7 cm. of polyethylene or rubber catheter is introduced into the ventricle. The posterior fossa is exposed until the cisterna magna is visualized. The catheter is passed subgaleally from the burr hole wound, entering the cisterna via a small slit. The catheter is then secured to the dura at both ends, patency is checked by injection of saline in both directions, and the wound is closed.

RESULTS

If the cisterna magna and sub-arachnoid spaces have never contained an adequate amount of fluid, they may not open up enough to carry the shunted fluid.

Groschel and Marguth have reported on the Torkildsen procedure as follows:[10]

85 supratentorial and 75 infratentorial stenoses were included in the survey. The shunt tube was placed epidurally instead of subgaleally to guarantee better support. The tube used was very thin to avoid local widening of the ventricle by movement of the drain, and seepage of cerebrospinal fluid into brain tissue with resulting necrosis.

Complication	Deaths
Primary Operative Mortality	48 (30%)
23 Meningeal Reactions and Meningitis	5
35 Central Respiratory & Cardiovascular Disturbances	35
23 Cerebrospinal Fluid Fistulas	21
	109 (70%)

Further analysis of 70 cases who survived the first year reveals the following:

—of 21 with craniopharyngioma:

9 died from later tumor resection
7 died from tumor progression
4 alive six years later, but neurologically damaged
1 able to work six years later

—of 23 with posterior third ventricle tumors:

2 died from later tumor resection
8 died from infection or failure of vegetative function
2 lost to follow-up
11 lead a normal life 2—8½ years later

—of 15 with aqueductal stenoses:

8 died from infection or failure of vegetative function
1 is an invalid due to neurological damage seven years post-operatively
6 are in good clinical condition 5-6 years later

—of 11 with infratentorial tumors:

5 died from infection or failure of vegetative function
6 are in good condition after one year

These statistics illustrate the type of complication that appears with shunt procedures, and will begin to appear with the ventriculo-caval and ventriculo-atrial shunts when more time has elapsed.

Thus, life can be significantly extended in about 30% of cases. Of this 30%, those with benign, inactive tumors, or with obstruction due to post-inflammatory adhesions, can expect a normal life. The Torkildsen shunt is, of course, only a palliative procedure in cases with malignant, inoperable tumors.

Ventriculo-caval and Ventriculo-atrial Shunts

INDICATIONS

These procedures are effective in the relief of both obstructive and communicating hydrocephalus.

DESCRIPTION

The Holter-Spitz shunt connects the lateral ventricle to the superior vena cava, and the Heyer-Pudenz type connects the lateral ventricle to the right atrium.

The Heyer-Pudenz Ventriculo-atrial Shunt

This consists of a tube inserted into the lateral ventricle through a burr hole 3-5 cm. superior and posterior to the external auditory meatus. This tube leads to a silicone dome flushing device, placed sub-cutaneously. It is connected to a venous catheter which runs via the common facial vein to the internal jugular vein, to end in the right atrium. There are multiple slit valves in the side wall of the atrial end to prevent the reflux of blood. The components are siliconed to be non-wettable and prevent clot or thrombus formation.

An advantage of having the end of the venous catheter in the right atrium is the prevention of thrombus formation by the fast-flowing blood.

The Holter-Spitz Ventriculo-caval Shunt

This device ends in the superior vena cava, and is fitted with a double-valve assembly between the ventricular and venous tubes. Otherwise the principle is that of the Heyer-Pudenz shunt.

With this valve, the patency of either end can be tested. If the connecting tube cannot be compressed, then the caval end is blocked. If the tube does not re-fill after compression, then the cranial end is blocked. The valve is also designed to open at various pressures. In advanced cases of hydrocephalus, a fairly high pressure valve is used. If fluid is allowed to escape rapidly through a low pressure valve, the acute decompression could cause a fatal herniation.

In both shunt types, the ventricular and cardiac or caval ends are impregnated with metallic powder for x-ray localization.

COMPLICATIONS AND PROGNOSIS

Long-range figures are not yet available, but a few small surveys have made the following complications evident: plugging of the ventricular catheter by brain fragments dislodged on introduction; thrombosis of the superior vena cava or jugular vein; ventriculitis, cerebrospinal fluid fistulas; meningitis.

Yashon and Sugar[11] reported on 50 cases—31 Holter-Spitz devices and 19 Heyer-Pudenz:

12 died
13 doing poorly
25 doing well

Cassinari[12] says "For non-neoplastic hydrocephalus, the Holter-Spitz shunt allowed control of hydrocephalus in 30 of 42 cases".

Carrington[13] reported on 50 patients followed from 2 to 18 months:

10 revisions in 8 patients
43 clinically well

Hendrick[14] reports that 68% of communicating hydrocephalus cases and 50% of those with obstructive hydrocephalus are well 11 years after a ventriculo-atrial or ventriculo-caval shunt.

D. S. Palframan

ACKNOWLEDGEMENT

I would like to acknowledge the assistance of Dr. E. B. Hendrick of the Toronto Hospital for Sick Children for his assistance in preparing this Article.

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(Continued from page 123)

physiological mechanisms. Only one specific disease—facial hemiatrophy, is sometimes identified as Romberg's disease.

The astute neurologist produced a second edition of his text in 1853 and in the preface was forced to confess that the hope expressed earlier for the future of neurology had been only partially fulfilled in the interval. He wrote:

"The study of nervous diseases, which some persons have refused to acknowledge as anything but the manifestation of other morbid processes, has been declared a fruitless research, and in some schools has been almost interdicted. . . . To guard against further debasement upon the new path opened to us, let our guide be the analysis of observation, not the cavilling spirit which even attacks the solid basis of physiological laws, such as the law of accentrical phenomena, or the law prohibiting one nerve from acting on another,—but the purifying criticism which lays bare defects, and mercilessly eradicates fallacies and untruths."

The classification of Romberg was slowly abandoned, as specific neurological and neuromuscular entities were recognized and the pathogenesis of some revealed. His physiologcial principles that were the basis for classification, however, were sound and his treatise was the first modern compendium of nervous diseases.

Romberg died in 1873, but the sign and his analytical approach are still part of present day neurology.

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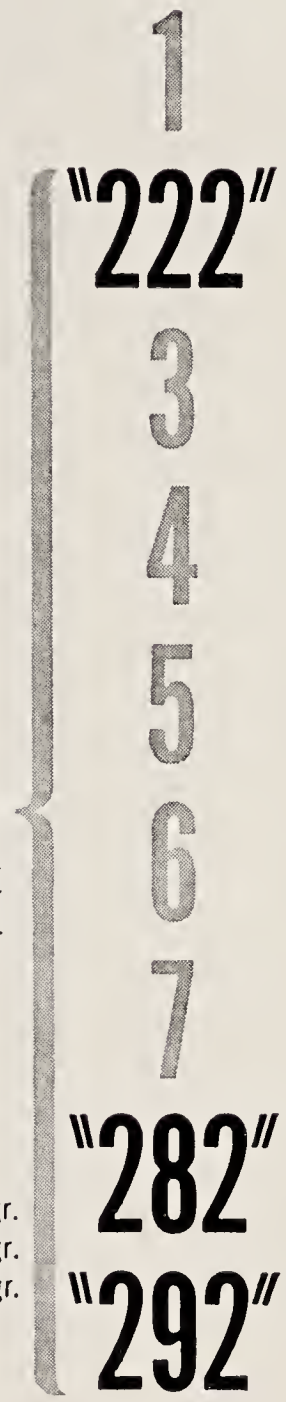

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